Mepolizumab versus placebo for asthma

Review information

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Abstract

Background
Mepolizumab is a human monoclonal antibody against interleukin-5 (IL-5), the main cytokine involved in the activation of eosinophils, which in turn causes airway inflammation. Recent studies have suggested these agents may have a role in reducing exacerbations and improving health-related quality of life (HRQoL). There are no recommendations for the use of mepolizumab in adults or children in the recent update of the BTS/SIGN guidelines (BTS/SIGN 2014).

Objectives
To compare the effects of mepolizumab with placebo on exacerbations and HRQoL in adults and children with chronic asthma.

Search methods
We searched the Cochrane Airways Group Register (CAGR) of trials, clinical trial registries, manufacturers’ websites and the reference lists of included studies. Searches were conducted in November 2013 and updated in November 2014.

Selection criteria
We included randomised controlled trials comparing mepolizumab versus placebo in adults and children with asthma.

Data collection and analysis
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Two authors independently extracted data and analysed outcomes using a random-effects model. We used standard methods expected by The Cochrane Collaboration.

**Main results**

Eight studies on 1707 participants met the inclusion criteria. Only two studies included children (over 12 years of age), but they did not report separate findings for the adolescents. Seven studies involved intravenous mepolizumab alone; one included a subcutaneous arm. There was heterogeneity in the severity and clinical pattern of asthma among the participants in the eight studies, varying from mild to moderate atopic asthma, to persistent asthma and eosinophilic asthma with recurrent exacerbations. Selection bias was a concern in several of the studies included in this review.

Four trials compared intravenous mepolizumab to placebo in relation to HRQoL. Two studies measured scores from the Asthma Quality of Life Questionnaire (AQLQ), which showed a non-significant difference between mepolizumab and placebo (mean difference (MD) 0.21, 95% confidence interval (CI) −0.01 to 0.44; participants = 682), in the direction favouring mepolizumab. The third study used the St. George's Respiratory Questionnaire (SGRQ) and found a significant difference between mepolizumab and placebo (MD 6.40, 95% CI 3.15 to 9.65; participants = 576), which indicated a clinically important benefit favouring mepolizumab. A fourth study noted that there was no significant difference but did not provide any data.

The two studies in people with eosinophilic asthma showed a reduction in clinically significant exacerbation rates (Risk Ratio 0.52, 95% CI 0.43 to 0.64; participants = 690). However, an analysis of four studies that were not confined to people with eosinophilic asthma indicated considerable heterogeneity and no significant difference in people with one or more exacerbations between mepolizumab and placebo using a random-effects model (Risk Ratio 0.67, 95% CI 0.34 to 1.31; participants = 468; I² = 59%). The analysis of serious adverse events indicated a significant difference favouring mepolizumab (Risk ratio 0.49, 95% CI 0.30 to 0.80; participants = 1441; studies = 5; I² = 0%). It was not possible to combine the results for adverse events, and we deemed the quality of this evidence to be low.

A single study compared subcutaneous mepolizumab to placebo in 385 adults with severe eosinophilic asthma and found an improvement in HRQoL scores and a reduction in asthma exacerbations, including exacerbations requiring admission to hospital.

**Authors’ conclusions**

It is not possible to draw firm conclusions from this review with respect to the role of mepolizumab in patients with asthma. Our confidence in the results of this review are limited by the fact that the intravenous route is not currently licensed for mepolizumab, and the evidence for the currently licenced subcutaneous route is limited to a single study in participants with severe eosinophilic asthma.

The currently available studies provide evidence that mepolizumab can lead to an improvement in health-related quality of life scores and reduce asthma exacerbations in people with severe eosinophilic asthma. Further research is needed to clarify which subgroups of patients with asthma could potentially benefit from this treatment. Dosage, ideal dosing regimens and duration of treatment need to be clarified, as the studies included in this review differed in their protocols. There are no studies reporting results from children, so we cannot comment on treatment for this age group. At the present time, larger studies using licenced treatment regimens are required to establish the role of mepolizumab in the treatment of severe asthma.

**Plain language summary**

**Mepolizumab as opposed to placebo for asthma**

**Review question**

We considered in this review whether taking mepolizumab is better than a placebo for people with asthma.

**Background**

Asthma is an inflammatory lung condition characterised by the narrowing of the airways, breathlessness, a tight chest and reduced quality of life. By the year 2025, there may be up to 400 million people with asthma worldwide. Mepolizumab is one treatment that may help to reduce the symptoms.

**Study characteristics**

Eight studies compared mepolizumab treatment to a placebo in 1707 patients with asthma. Six studies only included adults. We summarised the results as they relate to quality of life, occurrence of asthma attacks needing hospital admission and side effects of mepolizumab.

**Key results**

We found that patients with severe asthma who had high levels of eosinophils (inflammatory cells in the blood stream) benefited from taking mepolizumab through improved quality of life and reduced asthma attacks. There was no benefit in terms of lung function. We have avoided making recommendations because we think that further research is needed to clarify aspects such as dosage and length of treatment as well as which patients might benefit the most.

**Background**

**Description of the condition**

A recent global estimate of the number of people currently suffering from asthma is in the region of 300 million, and it is...
expected that by 2025 the number will increase to 400 million (WHO 2007). The subsequent burden of disease is likely to continue to impose additional pressures on patients, their families and healthcare systems (Masoli 2004). The increased incidence in morbidity has been associated with suboptimal delivery of care, including under-treatment with corticosteroids and a limited awareness of the condition amongst patients (Gibson 1993; Kandane-Rathayake 2009).

In the USA, the number of people with asthma increased from 20 million in 2001 to 25 million in 2009 (CDC 2011). Prevalence rates are slightly higher among children (10%) than among adults (8%) (CDC 2011; CDC 2012), with considerable variation among different ethnic groups. Between 2008 and 2010, asthma prevalence rates in the USA were 14.1% among multiracial individuals, 11.2% among blacks, 9.4% among Alaska Natives, 9.4% among other Native Americans, 7.7% among whites and 5.2% among those of Asian descent (CDC 2011). Globally, the prevalence of wheezing symptoms in children varies geographically, with the UK having the highest recorded prevalence of current wheezing at 32.3% and Ethiopia the lowest at 1.7% (Patel 2008).

For many people, asthma has an important impact on quality of life (Clayton 2005) and on financial considerations (Wu 2007). In the USA, approximately 10 million people experience asthma exacerbations each year (Krishnan 2006), and in the UK, over 65,000 hospital admissions for asthma were recorded in 2005 and 2006 (NHS 2011).

In recent years, clinical guidelines have been produced for the management of asthma at national (e.g. BTS/SIGN 2014; NIH 2007) and international (GINA 2012) levels. Several risk factors for asthma have been identified, including triggers such as allergens, chemical irritants and tobacco smoke, but asthma-related mortality and morbidity remain a major health concern (Braman 2006). On the other hand, the condition can also be controlled and health-related quality of life (HRQoL) maintained for considerable periods (WHO 2011).

**Description of the intervention**

One of the core pathological features of asthma is considered to be eosinophilic infiltration of the bronchial mucosa, which triggers an inflammatory response. Mepolizumab is a humanised monoclonal antibody against interleukin-5 (IL-5) that has been shown to inhibit eosinophilic airway inflammation. A number of studies have been conducted in young adults (> 12 years old) and adults with recurrent severe asthma exacerbations and signs of eosinophilic inflammation (Haldar 2009; Nair 2008; Pavord 2012). The results of these studies suggest that inhibiting eosinophilic inflammation by monoclonal antibodies may be associated with a reduced risk of acute exacerbations of asthma and a reduction in eosinophil count.

**How the intervention might work**

Proteins secreted by eosinophils cause damage to the epithelium, initiating vasodilatation, smooth muscle contraction and increased mucous secretion, which in turn is associated with increased airway hyperresponsiveness, asthma symptoms and airway narrowing (Liu 2013).

Mepolizumab is a key monoclonal antibody inhibiting IL-5, which is the main cytokine involved in eosinophil activation and recruitment. This intervention might work by preventing the initiation of the inflammatory response. Mepolizumab is administered intravenously as either a one-off dose of 2.5 to 10 mg/kg or monthly doses of 75 mg, 250 mg or 750 mg given for a period ranging from 16 to 52 weeks. Mepolizumab can also be given subcutaneously.

**Why it is important to do this review**

In a recently published meta-analysis of seven randomised placebo-controlled trials on 1131 adults, mepolizumab was shown to reduce the risk of exacerbations and improve quality of life in people with eosinophilic asthma, but did not lead to a significant improvement in lung function (Liu 2013).

It is important to do this review so that the evidence presented and the judgements made in Liu 2013 are available and placed in context within The Cochrane Library. Our review will also set the stage for future updates as more evidence becomes available.

**Objectives**

To compare the effects of mepolizumab with placebo on exacerbations and HRQoL in adults and children with chronic asthma.

**Methods**

**Criteria for considering studies for this review**

**Types of studies**

We included randomised controlled trials (RCTs). We included studies reported as full text, those published as abstracts only and unpublished data. Included trials were a minimum of 16 weeks in duration.

**Types of participants**

We included both adults and children with a diagnosis of asthma. We focused on collating data from people who have been reported as having eosinophilic asthma to analyse these individuals as a subgroup. We examined individual articles in order to determine how this group should be defined.

Individuals with congenital heart disease and respiratory comorbidities such as cystic fibrosis were excluded, as were current smokers.

**Types of interventions**
We included trials comparing mepolizumab with placebo. We planned to include the following cointerventions provided they were not part of the randomised treatment: leukotriene antagonists, inhaled bronchodilators (including long-acting beta$_2$-agonists), systemic and inhaled steroids, oral aminophylline and macrolide antibiotics. Studies that initiated a reduction in standard asthma management as part of the protocol were excluded. Nair 2009 included a reduction in the dose of prednisolone in the second phase of the trial. Therefore, only phase one of this trial was included as patients remained on their standard asthma treatment during this four-week period.

**Types of outcome measures**

**Primary outcomes**
1. HRQoL (as measured by a validated questionnaire)
2. Asthma exacerbation as defined by a hospital admission or treatment with a course of oral corticosteroids
3. Serious adverse events

**Secondary outcomes**
1. Measures of lung function: forced expiratory flow in one second (FEV$_1$), peak expiratory flow rate (PEFR)
2. Asthma symptoms
3. Adverse events/side effects
4. Eosinophil counts in peripheral blood, sputum or bronchoalveolar lavage fluid

Reporting one or more of the outcomes listed here in the trial was not an inclusion criterion for the review.

**Search methods for identification of studies**

**Electronic searches**
We identified trials from the Cochrane Airways Group Specialised Register (CAGR), which is maintained by the Trials Search Co-ordinator for the Group. The Register contains trial reports identified through systematic searches of bibliographic databases, including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO. We also handsearched respiratory journals and meeting abstracts (please see Appendix 1 for further details). We searched all records in the CAGR using the search strategy in Appendix 2.

We also conducted a search of ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/).

We searched all databases from their inception to the present and imposed no restriction on language of publication. The search was first conducted in November 2013 and was updated in November 2014.

**Searching other resources**
We checked the bibliographies of all primary studies and review articles for additional references. We searched relevant manufacturers' websites for trial information.

We searched for errata and retractions relevant to the included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and planned to report the date this was done within the review if this was an issue.

**Data collection and analysis**

**Selection of studies**
Two review authors (NW, CP) independently screened titles and abstracts of all the potential studies identified in the search and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved the full-text study reports/publications, and two review authors (NW, CP) independently screened the full text and identified studies for inclusion, identifying and recording reasons for excluding the ineligible studies. We planned to resolve any disagreement through discussion or, if required, by consulting a third author (SJM); however, this was not necessary. We identified and excluded duplicates and collated multiple reports of the same study so that each study rather than each report was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and a 'Characteristics of excluded studies' table.

**Data extraction and management**
We used a data collection form to record study characteristics and outcome data that had been piloted on at least one study in the review. Two review authors (LB, NW) extracted the following study characteristics from included studies.

1. Methods: study design, total duration of study, details of any run-in period, number of study centres and location, study setting, withdrawals and date of study.
2. Participants: number, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria and exclusion criteria.
3. Interventions: intervention, comparator, concomitant medications and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial and notable conflicts of interest of trial authors.

Two review authors (LB, NW) independently extracted outcome data from included studies. We noted in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We planned to resolve disagreements by consensus or by involving a third author (CP), but this was not necessary. One review author (KD) transferred data into
Review Manager (RevMan). We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (SJM) spot-checked study characteristics for accuracy against the trial report.

**Assessment of risk of bias in included studies**

Two review authors (LB, NW) independently assessed risk of bias for each study using the criteria outlined in the "Cochrane Handbook for Systematic Reviews of Interventions" (Higgins 2011). We planned to resolve any disagreements by discussion or by involving another author (SJM), but this was not necessary. We assessed the risk of bias according to the domains:

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessment;
5. incomplete outcome data;
6. selective outcome reporting;
7. other bias.

We graded each potential source of bias as high, low or unclear, and provided a quotation from the study report together with a justification for this judgement in the 'Risk of bias' table. We summarised the risk of bias judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes where necessary (e.g. for an unblinded outcome assessment, risk of bias for all-cause mortality may be very different than that for a patient-reported pain scale). Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.

When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

We conducted the review according to this published protocol and have reported any deviations from it in the 'Differences between protocol and review' section of the systematic review.

**Measures of treatment effect**

We analysed dichotomous data as risk ratios and rate ratios and continuous data as mean differences or standardised mean differences, which are presented with 95% confidence intervals. We entered data presented on a scale with a consistent direction of effect. However, on one occasion we had to use the risk ratio as one study had reported this (Haldar 2009).

We have undertaken meta-analyses only where this was meaningful (i.e. if the treatments, participants and underlying clinical question were sufficiently similar for pooling to make sense).

Where multiple trial arms were reported in a single trial (Flood-Page 2007; Pavord 2012), we combined the relevant arms (750 mg, 250 mg, 75 mg in Pavord 2012 and 750 mg, 250 mg in Flood-Page 2007) when appropriate.

In future updates of this review, we will narratively describe skewed data reported as medians and interquartile ranges. Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) are combined in the same meta-analysis, we will halve the control group to avoid double-counting.

**Unit of analysis issues**

No cross-over studies or cluster randomised trials were identified for inclusion in this version of the review. If cross-over trials are identified in the future, data from a paired analysis will be sought from the trial report or authors in order to appropriately include data in the review using the inverse variance method. If cluster randomised trials are identified in the future, then analyses will be at the level of the individual while allowing for the clustering in the data by using the intracluster correlation coefficient. If this is not reported in the trial, then it will be imputed from similar studies.

**Dealing with missing data**

Although unnecessary for this version of the review, we may contact investigators or study sponsors for future versions in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as an abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

**Assessment of heterogeneity**

Statistical heterogeneity between studies was assessed visually by inspection of the forest plots and using the Chi² test (a P value < 0.10 was considered significant due to the low power of the test). The I² statistic was also calculated; this describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). Values of I² range from 0% to 100%, with 0% representing no heterogeneity and 100% representing considerable heterogeneity.

For this review, heterogeneity as reported using the I² statistic was defined as follows.

- 0% to 40%: heterogeneity might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: considerable heterogeneity.
Assessment of reporting biases
If we are able to pool more than 10 trials for future versions, we will create and examine a funnel plot to explore possible small study biases and publication bias.

Data synthesis
In view of the considerable clinical heterogeneity between the included studies, we used a random-effects model. Data on outcomes were combined at 6 months and 12 months. Where data for other time points were reported, these were also described.

Subgroup analysis and investigation of heterogeneity
Provided sufficient studies were included, we planned to carry out subgroup analyses according to:
1. age (0 to 5 years, 6 to 16 years, 17 years and older);
2. eosinophilic individuals versus non-eosinophilic individuals; and
3. dose of intervention (posthoc subgroup identified);

using the outcomes:
1. HRQoL; and
2. asthma symptoms.

If more studies are included in the future, we will use the formal test for subgroup interactions in RevMan.

Sensitivity analysis
We planned to carry out the following sensitivity analyses if sufficient studies were included.
1. Excluding studies with an overall high risk of bias.
2. Excluding cross-over trials and cluster randomised trials.

Summary of findings table
We created 'Summary of findings' tables using the following outcomes.
1. HRQoL.
2. Asthma exacerbation as defined by a hospital admission or treatment with a course of oral corticosteroids.
3. Serious adverse events.

We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes. We used methods and recommendations described in Section 8.5 and Chapter 12 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011) using GRADEpro software. We have justified all decisions to downgrade or upgrade the quality of studies using footnotes, and we have made comments to aid the reader's understanding of the review where necessary.

Results
Description of studies
Results of the search
We identified 154 records in our literature searches: 129 in database searches in November 2013 and a further 25 in November 2014 (Figure 1). Eight studies met our inclusion criteria ('Characteristics of included studies' table), and two others were included in the ongoing studies category ('Characteristics of ongoing studies' table). The eight included studies had 25 records: one for Buttnert 2003; seven for Flood-Page 2003, one for Flood-Page 2007, four for Haldar 2009, one for Leckie 2000; five for Nair 2009; two for Ortega 2014 and four for Pavord 2012. The remaining 127 records were excluded for various reasons ('Characteristics of excluded studies' table).

Included studies
We included eight studies ('Characteristics of included studies' table), involving 1707 total participants distributed as follows: Buttnert 2003, 19; Flood-Page 2003, 24; Flood-Page 2007, 362; Haldar 2009, 61; Leckie 2000, 24; Nair 2009, 20; Ortega 2014, 576 Pavord 2012, 621. Table 1 compares the design, numbers, interventions and patient groups in the included trials. The severity of asthma among participants varied from mild atopic asthma to persistent eosinophilic asthma with recurrent exacerbations. The mepolizumab was administered exclusively through intravenous route in seven of the studies, with dosage varying from 2.5 mg/kg or 10 mg/kg, or 75 mg, 250 mg and 750 mg with different dosing regimens over a range of treatment periods. Only one study had a subcutaneous (SC) arm, with a dose of 100 mg (Ortega 2014).

Excluded studies
We excluded 127 records from the review. Of these, 119 (94%) were excluded because mepolizumab had not been included in the study, 4 (3%) were excluded because they did not include a placebo arm, another 2 (2%) were excluded because the focus was on steroid reduction, 1 (1%) was non-randomised, and the remaining study (1%) was conducted on healthy participants without a diagnosis of asthma ('Characteristics of excluded studies' table).

Risk of bias in included studies
Details of our risk of bias assessments are available in the ‘Characteristics of included studies’ table, and a summary of our assessment can be seen in Figure 2 and Figure 3.

Allocation (selection bias)
We deemed only three studies (Nair 2009; Pavord 2012; Ortega 2014) to be at low risk of bias for both random sequence generation and allocation concealment. We judged Haldar 2009 to be at low risk of bias for random sequence generation, but its bias with regard to allocation concealment was unclear. The risk of bias for the remaining four studies (Buttner 2003; Flood-Page 2003; Flood-Page 2007; Leckie 2000) was unclear for both random sequence generation and allocation concealment (Figure 3).

Blinding (performance bias and detection bias)
With regard to performance bias and detection bias, we determined that all eight studies were at low risk of bias (Figure 3).

Incomplete outcome data (attrition bias)
In terms of attrition bias, we considered seven of the studies to be at low risk of bias, while the risk of bias in Buttner 2003 was unclear (Figure 3).

Selective reporting (reporting bias)
One study noted that there was no significant difference in HRQoL but did not provide any data (Flood-Page 2007), so we considered it to be at high risk of bias. We deemed all other studies to be at low risk of bias as there was no apparent evidence of selective reporting.

Effects of interventions
Primary outcomes
HRQoL (as measured by a validated questionnaire)
Three studies (participants = 1044) measured quality of life using the Asthma Quality of Life Questionnaire (AQLQ) (Flood-Page 2007; Haldar 2009; Pavord 2012). One study noted that there was no significant difference but did not provide any data (Flood-Page 2007).

Intravenous mepolizumab versus placebo
Pavord 2012 reported data at 52 weeks for three different dose groups of Intravenous (IV) mepolizumab (75 mg, 250 mg, 750 mg), which we combined and presented as one group. Haldar 2009 reported data at 50 weeks. Combining the two studies, Analysis 1.1 showed a non-significant difference between IV mepolizumab and placebo (MD 0.21, 95% CI − 0.01 to 0.44; participants = 682), favouring IV mepolizumab. Our confidence in this result is low, as the mean difference is less than the clinical minimally important difference of 0.5 units, and no responder analysis is reported (Summary of findings table 1).

Ortega 2014 measured quality of life using the St. George’s Respiratory Questionnaire (SGRQ) and found a significant difference favouring IV mepolizumab over the placebo (MD 6.40, 95% CI 3.15 to 9.65; participants = 382; Analysis 1.2). We only have moderate confidence in this result, as IV delivery is not currently a licenced route of administration for mepolizumab (Summary of findings table 1).

Subcutaneous mepolizumab versus placebo
Ortega 2014 measured quality of life using the St. George’s Respiratory Questionnaire (SGRQ) and found a significant difference between subcutaneous (SC) mepolizumab and placebo, in favour of mepolizumab (MD − 7.00, 95% CI − 10.19 to − 3.81; participants = 385; Analysis 2.1). We have moderate confidence in this result from a single study (Summary of findings table 2).

Asthma exacerbation as defined by a hospital admission or treatment with a course of oral corticosteroids
Six studies (participants = 1664) reported on asthma exacerbations (Flood-Page 2003; Flood-Page 2007; Haldar 2009; Nair 2009; Pavord 2012; Ortega 2014). Increase in oral corticosteroids is included in the definition of exacerbation for three studies (Haldar 2009; Ortega 2014; Pavord 2012). Two studies did not include an increase in oral corticosteroids in the definition of exacerbation (Flood-Page 2007; Nair 2009), while one study did not provide a definition of exacerbation (Flood-Page 2003).

IV Mepolizumab versus placebo
Four studies (Flood-Page 2003; Flood-Page 2007; Haldar 2009; Nair 2009) reported the number of patients experiencing an exacerbation. Analysis 1.6, which used a random-effects model, did not show a significant difference between IV mepolizumab and placebo (Risk Ratio 0.67, 95% CI 0.34 to 1.31; participants = 468 I2 = 59%). Our confidence in this result is low due to the wide confidence intervals (Summary of findings table 1).

Pavord 2012 reported the rate ratio of exacerbations for each of the three different dose groups of IV mepolizumab compared to placebo. Ortega 2014 reported the percentage reduction in the rate ratio for clinically significant exacerbations for 75 mg IV mepolizumab compared to placebo. We combined the results for groups taking the 75 mg dose from these studies, both of which included participants with severe eosinophilic asthma.

Analysis 1.3 shows similar results for the rate of clinically significant exacerbations, which include a course of oral steroids, emergency department (ED) visit or admission. For the 75 mg dose, the rate of ED visits or hospital admissions for people on mepolizumab was half that of the placebo group (rate ratio 0.52, 95% CI 0.43 to 0.64; participants = 690; studies = 2). For the 250 mg dose, the result was similar (rate ratio 0.61, 95% CI 0.46 to 0.81; participants = 307; studies = 1) and also for the
750 mg dose (rate ratio 0.48, 95% CI 0.36 to 0.64; participants = 311; studies = 1). Our confidence in this result is moderate, as IV delivery is not currently a licenced delivery route for mepolizumab (Summary of findings table 1).

**Analysis 1.4** shows the rate ratio for the combined results of these two studies in terms of exacerbations requiring hospital admission, and there is not a significant difference for the 75 mg mepolizumab dose (rate ratio 0.61, 95% CI 0.33 to 1.13; participants = 690; studies = 2). The 750 mg IV mepolizumab group compared to placebo showed a reduction in the risk of being admitted to hospital (rate ratio 0.37, 95% CI 0.16 to 0.86; participants = 311; studies = 1). The 250 mg dose did not show a statistically significant reduction (rate ratio 0.65, 95% CI 0.31 to 1.37; participants = 307; studies = 1), but the difference between doses was not significant (test for subgroup differences: \( \chi^2 = 1.14, \text{degree of freedom (df)} = 2 (P = 0.57), I^2 = 0\%\)).

**Analysis 1.5** shows the combined results on exacerbations requiring a visit to the ED or hospital admission. For the 75 mg dose, there was a significant reduction in the exacerbation rate for this outcome (rate ratio 0.52, 95% CI 0.31 to 0.87; participants = 690; studies = 2), and although the reduction in rate was similar for the other doses, it did not reach statistical significance (250 mg dose: rate ratio 0.58, 95% CI 0.30 to 1.12; participants = 307; studies = 1; and 750 mg dose: rate ratio 0.52, 95% CI 0.27 to 1.02; participants = 311; studies = 1). Again there was no significant difference between the results according to dose (test for subgroup differences: \( \chi^2 = 0.08, \text{df} = 2 (P = 0.96), I^2 = 0\%\)).

**SC Mepolizumab versus placebo**

**Ortega 2014** also found a reduction in the rate of all of the above types of exacerbations favouring SC mepolizumab in comparison to placebo. **Analysis 2.2** shows the results for hospital admission (rate ratio 0.31, 95% CI 0.11 to 0.91; participants = 385; studies = 1). **Analysis 2.3** shows the reduction in either ED visits or hospital admission (rate ratio 0.39, 95% CI 0.18 to 0.83; participants = 385; studies = 1). **Analysis 2.4** shows the reduction in clinically significant exacerbations (rate ratio 0.47, 95% CI 0.35 to 0.63; participants = 385; studies = 1). We have moderate confidence in these results from a single study (Summary of findings table 2).

**Serious adverse events**

Five studies (participants = 1640) reported information on serious adverse events. **Nair 2009** stated that there were no serious adverse events, while **Pavord 2012** reported that the overall frequency of serious adverse events was similar across treatment groups and that no serious life-threatening anaphylactic reactions were observed; however, three patients in the IV mepolizumab groups died during the study for reasons that the physician investigator judged to be unrelated to the treatment.

**Flood-Page 2007** reported nine serious adverse events: four in patients receiving placebo (vertigo, bladder carcinoma, unintended pregnancy and asthma exacerbation), three in patients receiving IV mepolizumab 250 mg (hydrocephalus/cerebrovascular disorder, constipation and gastrointestinal disturbance), and two in patients receiving IV mepolizumab 750 mg (asthma exacerbation). None of these serious adverse events was considered to be related to the study medication, and there were no significant differences between the treatment groups.

**Haldar 2009** reported that hospitalisation for asthma was a serious adverse effect for 10% (3/29) of participants in the IV mepolizumab arm and 34% (11/32) in the placebo arm.

**Ortega 2014** reported that the incidence of serious adverse events (including asthma-related events) was 7% in the intravenous mepolizumab group, 8% in the subcutaneous mepolizumab group, and 14% in the placebo group.

**Analysis 1.7** indicated that there was a significant difference between IV mepolizumab versus placebo (Risk Ratio 0.49, 95% CI 0.30 to 0.80; participants = 1441; studies = 5; \( I^2 = 0\%)\), favouring IV mepolizumab. Our confidence in this result is moderate, as IV delivery is not currently a licenced route of administration for mepolizumab (Summary of findings table 1).

**Secondary outcomes**

**Measures of lung function: forced expiratory flow in one second (FEV\(_1\)), peak expiratory flow rate (PEFR)**

Seven studies (participants = 1688) report on lung function (Flood-Page 2003; Flood-Page 2007; Haldar 2009; Leckie 2000; Nair 2009; Pavord 2012; Ortega 2014).

**IV Mepolizumab versus placebo**

**Flood-Page 2003** reported no difference between IV mepolizumab and placebo for median FEV\(_1\) and median PEFR at 12 weeks (Table 2).

**Flood-Page 2007** reported mean change from placebo for FEV\(_1\) (L) and PEFR L/min at weeks 12 and 20. **Analysis 1.8** indicates there was no significant difference in FEV\(_1\) between IV mepolizumab and placebo at week 20. **Analysis 1.9** shows a significant difference for IV mepolizumab 250 mg compared to placebo (MD 13.49; 95% CI 0.71 to 26.27), but not for the 750 mg compared to placebo group (MD 3.42, 95% CI = 9.40 to 16.24). However, the test for subgroup difference was not significant (\( \chi^2 = 1.19, \text{df} = 1 (P = 0.280), I^2 = 15.9\%)\).

**Haldar 2009** and **Nair 2009** reported no significant difference in post-bronchodilator FEV\(_1\) (L) between IV mepolizumab and placebo at one year and six weeks, respectively (Analysis 1.10). **Nair 2009** also reported no difference between IV mepolizumab and placebo for percentage predicted FEV\(_1\) after bronchodilation (Analysis 1.11).
Pavord 2012 found no significant difference between any dose of IV mepolizumab and placebo in pre-bronchodilator FEV₁ (mL) at one year (Analysis 1.13).

Leckie 2000 reports no significant difference between IV mepolizumab and placebo in late asthmatic reaction (maximum percentage fall in FEV₁) (Analysis 1.14).

Ortega 2014 reported a statistically significant difference favouring IV mepolizumab for both pre- and post-bronchodilator FEV₁ (MD 0.10 L; 95% CI 0.01 to 0.19); (MD 0.15 L, 95% CI 0.05 to 0.24). (Analysis 1.10; Analysis 1.12).

SC Mepolizumab versus placebo

Ortega 2014 reported a statistically significant difference favouring SC mepolizumab for both pre- and post-bronchodilator FEV₁ (MD 0.10, 95% CI 0.02 to 0.18; participants = 385; studies = 1 and MD 0.14, 95% CI 0.04 to 0.23; respectively) (Analysis 2.5; Analysis 2.6).

Asthma symptoms

Five studies (participants = 1640) measured asthma symptoms (Flood-Page 2007; Haldar 2009; Nair 2009; Pavord 2012; Ortega 2014).

IV Mepolizumab versus placebo

Flood-Page 2007 reported results at 20 weeks using the asthma summary symptom score. Nair 2009 reported data at 4 weeks using a symptom score, a cough score and the Juniper Asthma Cough Questionnaire (JACQ) score. Haldar 2009 reported data at one year using the visual analogue scale symptom score and a modified Juniper Asthma Control Score. Pavord 2012 reported data using the asthma control questionnaire at one year. Ortega 2014 reported data at 32 weeks using the five-item Asthma Control Questionnaire (ACQ-5).

There were no significant differences between IV mepolizumab at 250 mg or 750 mg and placebo using an asthma symptom score or the JACQ, but there was a significant difference between 75 mg and placebo (MD – 0.30, 95% CI – 0.55 to – 0.04; participants = 690; studies = 2; Analysis 1.15), although test for subgroup difference was again non-significant (Chi² = 0.81, df = 2 (P = 0.67), I² = 0%).

SC Mepolizumab versus placebo

There was also a statistically significant improvement in symptoms on SC mepolizumab compared to placebo (MD – 0.44, 95% CI – 0.64 to – 0.24; participants = 385; studies = 1); Analysis 2.7). However, there was no responder analysis, and this mean difference is less than the minimal clinically important difference of ~ 0.5 units.

Adverse events/side effects

Six studies (participants = 1664) reported adverse events (Flood-Page 2003; Flood-Page 2007; Haldar 2009; Nair 2009; Pavord 2012; Ortega 2014).

Flood-Page 2003 reported that all of the 24 volunteers completed the study without reporting adverse events.

Flood-Page 2007 reported that there were no significant differences between the treatment groups for any adverse events reported. The most common adverse events (at least 5% of participants in any treatment group) were upper respiratory tract infection, asthma, headache, rhinitis, bronchitis, sinusitis, viral infection, injury, back pain, nausea and pharyngitis.

Haldar 2009 reported that one patient withdrew due to rash after mepolizumab infusion.

Nair 2009 reported that one patient in the IV mepolizumab group withdrew because of increased shortness of breath, thought to be due to heart failure. One patient in the placebo group died six months after the study because of sudden cardiac arrest; one patient in the IV mepolizumab group reported aches and tiredness when prednisolone was reduced.

Pavord 2012 found that the most frequently reported adverse events were headache (27 (17%) individuals given placebo, 32 (21%) given 75 mg IV mepolizumab, 32 (21%) given 250 mg IV mepolizumab, and 32 (21%) given 750 mg IV mepolizumab) and nasopharyngitis (24 (15%), 34 (22%), 33 (22%), and 29 (19%) for the four groups, respectively). The most frequently reported drug-related adverse event was infusion-related reaction (e.g. non-allergic reactions), which was reported by 10 (6%) patients given placebo, 8 (5%) given 75 mg mepolizumab, 12 (8%) given 250 mg IV mepolizumab, and 19 (12%) given 750 mg IV mepolizumab. Hypersensitivity deemed to be possibly related to investigational product was reported by three patients (2%) given placebo, none given 75 mg IV mepolizumab, one (< 1%) given 250 mg IV mepolizumab, and two (1%) given 750 mg IV mepolizumab.

In the Ortega 2014 study, the overall incidence of adverse events during treatment was similar in the three groups (84% in the IV mepolizumab group, 78% in the SC mepolizumab group, and 83% in the placebo group). The most frequently reported adverse events were nasopharyngitis and headache. The incidence of adverse events that were considered by the study investigators to be related to a study drug was 17% in the IV mepolizumab group, 20% in the SC mepolizumab group, and 16% in the placebo group. The incidence of injection-site reactions was more frequent in the SC mepolizumab group (9%) than in the IV mepolizumab group or the placebo group (3% in each).

Eosinophil counts in peripheral blood, sputum or bronchoalveolar lavage fluid

All eight studies (participants = 1707) report on eosinophil counts (Buttner 2003; Flood-Page 2003; Flood-Page 2007; Haldar 2009; Leckie 2000; Nair 2009; Pavord 2012; Ortega 2014).
There were only two studies that included paediatric patients, down to the age of 12 years old (Flood-Page 2003).

Peripheral blood eosinophil counts, sputum eosinophil counts and eosinophil counts in bronchoalveolar fluid all showed a not possible. regimens and protocols, direct comparison of eosinophil counts in peripheral blood, sputum and bronchoalveolar fluid was

placebo, in participants with severe eosinophilic asthma. There were minimal significant adverse events related to

mg IV mepolizumab and placebo (although a non-significant test for subgroup difference) and between SC mepolizumab and

increase in serious adverse events on treatment.

The results suggest that mepolizumab leads to an improvement in HRQoL and a reduction in asthma exacerbation rates for

people with severe eosinophilic asthma randomised to received mepolizumab compared to placebo, with no significant

increase in serious adverse events on treatment.

With regard to the secondary outcome measures, mepolizumab did not lead to a significant increase in measures of lung function (FEV1 or PEFR). There was no significant difference in asthma symptoms using an asthma symptom score or the

JACQ between IV mepolizumab at 250 mg or 750 mg and placebo. However, there was a significant difference between 75 mg IV mepolizumab and placebo (although a non-significant test for subgroup difference) and between SC mepolizumab and placebo, in participants with severe eosinophilic asthma. There were minimal significant adverse events related to mepolizumab, but headache and nasopharyngitis were commonly reported side effects. Due to the variety of dosing regimens and protocols, direct comparison of eosinophil counts in peripheral blood, sputum and bronchoalveolar fluid was not possible.

Peripheral blood eosinophil counts, sputum eosinophil counts and eosinophil counts in bronchoalveolar fluid all showed a significant reduction after treatment with mepolizumab.

There were only two studies that included paediatric patients, down to the age of 12 years old (Ortega 2014; Pavord 2012).
but there was no separate reporting of results in adolescents, so we have insufficient evidence to undertake a subgroup analysis based on age.

**Overall completeness and applicability of evidence**

Although the precise definition of asthma exacerbation is subject to debate, with the consequent variability in reporting, it is nevertheless considered to be one of the core outcomes to be measured in asthma studies (Fuhlbrügge 2012). We found evidence of a reduction in the rate of clinically significant exacerbations in adults with severe eosinophilic asthma given IV or SC mepolizumab. Health-related quality of life (HRQoL) improved with intervention compared to placebo by a mean of seven units in the single study using SGRQ (Ortega 2014), but the mean change in AQLQ was less than the minimal clinically important difference and was not accompanied by responder analyses. These two primary outcomes are clinically important outcomes for the individual. Secondary outcomes of asthma symptoms scores, cough scores, lung function and airway hyperreactivity were not influenced by mepolizumab. Most studies examined eosinophils, inflammatory markers and mediators using a combination of peripheral blood, sputum and bronchoalveolar lavage and showed reductions in those who received mepolizumab. The clinical relevance of this finding to patients may not be clinically important. There were no studies in children under 12 and only two studies included children aged 12 years or older (but without disaggregating results for the participating adolescents). The asthma population examined in this review was too heterogeneous to draw any conclusions about the general asthma population.

**Quality of the evidence**

Using the GRADE system, we considered the quality of evidence for IV mepolizumab to be limited, as this is not a licenced delivery route (so we would regard this as indirect evidence). We felt that the HRQoL results were of moderate quality, and further research may have an important effect on the results presented. There was a risk of reporting bias in the assessment of HRQoL for one paper: Flood-Page 2007 noted no significant changes in HRQoL but did not provide any data, thus no data could be included in the meta-analysis. We are aware of the limitations in some of the studies and have detailed them in the results section, Figure 2 and Figure 3. We determined that the risk of performance bias and detection bias based on the blinding processes was low in all eight studies. We also found that selection bias was low in only three studies for both random sequence generation and allocation concealment (Nair 2009; Ortega 2014; Pavord 2012) but unclear in four others (Buttner 2003; Flood-Page 2003; Flood-Page 2007; Leckie 2000). Haldar 2009 had a low risk of bias for random sequence generation, but the risk of bias was unclear with respect to allocation concealment. Publication bias was not formally assessed through the construction of a funnel plot due to the small number of included studies. However, we performed a thorough search strategy, including searching conference abstracts and ongoing studies, in order to identify unpublished studies.

**Potential biases in the review process**

We acknowledge the potential for publication bias in this review, as it is possible that we failed to identify unpublished trials that may have provided positive or negative outcomes, which in turn could have altered the treatment benefits. However, to the best of our knowledge, we identified a significant number of trials meeting our inclusion criteria through comprehensive and systematic database searches. We tried to address any study selection bias by having two review authors who independently evaluated all the identified studies. We also ensured that the assessment of each trial was consistently in line with the inclusion criteria.

**Agreements and disagreements with other studies or reviews**

Our review follows on from Liu 2013, which also considered the efficacy of mepolizumab in patients with asthma. The present review includes one extra study (Ortega 2014), and its findings are consistent with Liu 2013. Both reviews highlight the need for further research in this area.

**Authors' conclusions**

**Implications for practice**

It is not possible to draw firm conclusions from this review with respect to the role of mepolizumab versus placebo in patients with asthma, due partly to the heterogeneity of the studies. The currently available studies provide evidence that mepolizumab leads to an improvement in health-related quality of life scores and a reduction of asthma exacerbations in people with severe eosinophilic asthma (Haldar 2009; Nair 2009; Pavord 2012; Ortega 2014). There was also an improvement in asthma symptom scores in subjects with persistent eosinophilic asthma when using subcutaneous mepolizumab and 75 mg mepolizumab intravenously (Ortega 2014). Mepolizumab did not lead to a significant increase in measures of lung function.

Further research is needed to clarify which subgroups of patients with asthma could potentially benefit from this treatment. Dosage, ideal dosing regimens and duration of treatment need to be clarified, as the studies included in this review differed in their protocols. There were only two studies that included children (over the age of 12), and these do not provide sufficient evidence on which to base a recommendation for use. At the present time, larger studies are required to establish the role of mepolizumab in the treatment of asthma.

**Implications for research**

There needs to be further research on mepolizumab in children, with a focus on the core outcomes of exacerbations and HRQoL but also asthma symptoms and lung function (in children who can perform respiratory function tests).

In adults, the evidence available so far suggests that there is an improvement in HRQoL and frequency of acute
exacerbations in participants with severe eosinophilic asthma. However, there needs to be further research to ascertain the optimum dose and regimen for mepolizumab therapy, as the studies included in this review used a wide range of dosing regimens.

Acknowledgements
We would particularly like to acknowledge the excellent support and assistance from Emma Welsh, Liz Stovold and Emma Jackson of the Cochrane Airways Review Group, together with the greatly appreciated guidance from Chris Cates (Cochrane Airways Review Group Co-ordinating Editor). The support provided by librarians Judith Scammel, Jane Appleton and Hilary Garrett at St George's University of London is also greatly appreciated.

We are very grateful to Chris Cates, the Contact Editor who commented critically on the review.

The information provided by Prof Peter Barnes regarding an included study (Leckie 2000) is also much appreciated.

The background and methods section of this review is based on a standard template used by Cochrane Airways Group.

Contributions of authors
SM, KD, NW and CP contributed to the writing of the protocol. NW and CP independently selected trials for the review, NW and LB extracted the data, and KD entered the data into the RevMan file with cross-checking by SM. KD and SM wrote the Results section, and NW, LB, CP, KD and SM coauthored the Discussion and Conclusions.

Declarations of interest
None known.

Differences between protocol and review
We initially planned to use a fixed-effect model for meta-analysis, but we agreed with a peer reviewer who suggested that a random-effects model was more appropriate in view of the substantial clinical heterogeneity between the trials.

Although sufficient studies were not identified to conduct subgroup analyses, a posthoc subgroup analysis of dose of intervention was identified and included for use in a future version of this review.

We have included lung function and asthma symptoms in the summary of findings table as additional outcomes which we believe to be important to people making decisions about this intervention.

Published notes
Characteristics of studies
Characteristics of included studies
Buttner 2003
Methods

Randomised, placebo-controlled, parallel-group trial

Participants

Reported as: “Seven male and 12 female patients with mild or moderate asthma, aged 20–59 yrs (mean 41 yrs), with duration of disease between 1–32 yrs (mean 11 yrs) were investigated. For inclusion, FEV\textsubscript{1} had to be from 50 to 80% of predicted at baseline, with a reversibility of at least 12%. None of the patients suffered from clinical exacerbation, and all patients were on a stable daily dose of up to 1000 mcg beclomethasone dipropionate or a corresponding dose of other inhaled corticosteroids for at least 6 weeks prior to the study. As a symptom reliever salbutamol was allowed if needed. The detailed clinical characterisation of patients revealed no significant difference between the study groups.”

5 participants allocated to receive mepolizumab 750 mg, 7 to receive mepolizumab 250 mg and 7 to receive placebo.

Interventions

1 month run-in period to ensure stable disease
3 intravenous doses of either mepolizumab (750 mg), mepolizumab (250 mg) or placebo every 4 weeks with a follow-up period of 3 months

Outcomes

Peripheral blood leukocytes, qualitative and quantitative distribution of eosinophils and lymphocyte subpopulations, frequencies of IL-2, -3, -4, -5, -10, -13, interferon-c-producing CD4 T-cells and serum eosinophil cationic protein (ECP) levels

Notes

6-month multicentre trial in Germany
Supported in part by SmithKline Beecham, Harlow, UK

Risk of bias table

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Flood-Page 2003
Methods

| Participants | Reported as: "Twenty-four people with mild asthma, with a FEV\textsubscript{1} of 70% or more of predicted. Participants were within an 18- to 55-year-old age range. All were atopic (defined by a positive skin prick test to one or more aeroallergen), and all were well controlled with short-acting 2-agonists, without corticosteroids or other anti-inflammatory drugs in the preceding 8 weeks.

All participants had a clear history of asthma, demonstrated airway hyperresponsiveness with a PC\textsubscript{20} to histamine of 4.0 mg/mL or less. All were nonsmokers. Eleven participants received mepolizumab and 13 received placebo."

- Age: mepolizumab, median 31 years (range 20 to 53); placebo, median 30 years (range 20 to 52)
- Males: mepolizumab, 9; placebo, 8
- Baseline morning PEFR, L/min: mepolizumab, median 433 (range 358 to 585); placebo, median 459.5 (range 368 to 490)
- Baseline FEV\textsubscript{1}, L/s: mepolizumab, median 3.05 (range 2.55 to 4.85); placebo, median 3.1 (range 1.8 to 5.25)
- Baseline FEV\textsubscript{1}, % predicted: mepolizumab, median 87.0 (range 71 to 109); placebo, median 80.0 (range 71 to 106)

Interventions

- 3 Intravenous doses of either 750 mg of mepolizumab or placebo over 20 weeks (at weeks 0, 4 and 8)

Outcomes

Airway eosinophils, bone marrow eosinophils, blood eosinophils, airway hyperresponsiveness, FEV\textsubscript{1} and PEFR

Notes

20-week study conducted at the Royal Brompton and London Chest Hospitals, London UK.
Supported by GlaxoSmithKline.

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<td>All 24 volunteers completed the study without reporting adverse events or asthma exacerbations</td>
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Flood-Page 2007
### Methods
Multicentre, randomised, double-blind, placebo-controlled trial.

### Participants
Reported as: "Enrolled into the study were nonsmoking participants, aged 18–55 years, with asthma managed with inhaled corticosteroids (maximum dose of beclomethasone dipropionate (BDP) or equivalent, 1000 mcg/d). The FEV$_1$ had to be at least 50% and not more than 80% of the predicted value for age, sex, and height with documented beta$_2$-agonist reversibility of at least 12% after administration of 180 mcg of albuterol (salbutamol). The daily symptom score had to be at least 4 (maximum score, 12) during the 7 days preceding the baseline assessment. The principal exclusion criteria to ensure asthma stability and safety before dosing were as follows: an absolute FEV$_1$ value measured at randomisation (visit 3) that had changed by more than 20% from the value determined at a baseline signs-and-symptoms visit 2 weeks before dosing (visit 2); an upper respiratory tract infection in the 2 weeks before the first visit; use of oral corticosteroids in the 4 weeks before the first visit; or poorly controlled asthma, defined as hospitalisation or an emergency room visit for the treatment of asthma in the 6 weeks before the first visit."

- 116 allocated to receive mepolizumab 750 mg (112 completed), 120 to receive mepolizumab 250 mg (110 completed) and 126 to receive placebo (119 completed)
- Age (standard deviation (SD)): mepolizumab 750 mg, mean 36.3 years (±10.4), mepolizumab 250 mg, mean 35.8 years (± 10); placebo, mean 36.8 years (± 10)
- Males: mepolizumab 750 mg, 60; mepolizumab 250 mg, 52; placebo, 48
- Baseline ICS (beclomethasone) dose (mcg/d) (SD): mepolizumab 750 mg, mean 710 (± 381); mepolizumab 250 mg, mean 720 (± 448); placebo, mean 740 (± 486)
- Baseline morning mean PEFR (L/min) (SD): mepolizumab 750 mg, 375.7 (± 88.8); mepolizumab 250 mg 357.9 (± 90.6); placebo, 359.4 (± 90.4)
- Baseline mean FEV$_1$ (L) (SD): mepolizumab 750 mg, 2.51 (±0.58); mepolizumab 250 mg, 2.46 (± 0.56); placebo, 2.39 (± 0.59)
- Baseline mean (SD) FEV$_1$, % predicted: mepolizumab 750 mg, 68.3% (± 8.8%); mepolizumab 250 mg, 68.4% (± 9.6%); placebo, 68.4% (± 8.7%)
- Baseline mean (SD) FEV$_1$ reversibility: mepolizumab 750 mg, 24.5% (± 11.6%); mepolizumab 250 mg, 24.6% (± 12.1%); placebo, 25.1% (± 11.6%)

### Interventions
4-week run-in period to ensure stable disease
3 intravenous doses of mepolizumab (750 mg), mepolizumab (250 mg) or placebo (at weeks 0, 4 and 8)

### Outcomes
Reported as: "The primary efficacy variable was the change from baseline in domiciliary morning peak expiratory flow rate (PEFR) recorded at weeks 12 and 20. This was recorded as the mean PEFR over the 7 days preceding the treatment period (baseline value) and preceding weeks 12 and 20. The secondary efficacy variables were the changes from baseline of FEV$_1$, asthma summary symptom scores (the total of the daytime asthma, nighttime asthma, and morning asthma scores), use of rescue medication such as albuterol (salbutamol), quality of life scores, asthma exacerbation rates, and eosinophil counts in blood and sputum."

### Notes
20-week multicentre trial at 55 centres in 5 countries (France, Germany, Netherlands, the UK, and the USA)
Supported by GlaxoSmithKline.

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<td>Reported as: &quot;Of the 362 patients randomised into the study, a total of 21 patients (5.8%) were withdrawn. The percentage of patients completing the study was high for all treatment arms. The most common reason for withdrawal during the study was adverse experience (n=10; 2.8%). The percentage of patients who were withdrawn because of adverse experiences was higher among patients receiving placebo (4.0%) and mepolizumab at 250 mg (3.3%) compared with patients receiving mepolizumab at 750 mg (0.9%). A total of 37 patients were randomised to the induced sputum arm of the study, and 3 patients were subsequently withdrawn.&quot;</td>
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*Haldar 2009*
### Methods
Randomised, double-blind, placebo-controlled, parallel-group trial

### Participants
Participants had refractory eosinophilic asthma and a history of recurrent severe exacerbations.
Reported as: "Inclusion criteria were a diagnosis of refractory asthma according to American Thoracic Society criteria, a sputum eosinophil percentage of more than 3% on at least one occasion in the previous 2 years despite high-dose corticosteroid treatment, and at least two exacerbations requiring rescue prednisolone treatment in the previous 12 months. Additional criteria for inclusion were stable treatment requirements and an absence of exacerbations for more than 6 weeks before enrolment in the study. Exclusion criteria were current smoking, serologic evidence of a parasitic infection, a serious coexisting illness, the possibility of conception, and poor adherence to treatment."

- **Age:** mepolixumab, mean 48 (range from 21 to 63); placebo, mean 50 (range from 24 to 72)
- **Males:** mepolixumab, 14; placebo, 18
- **Baseline mean (SD) FEV$_1$, % predicted after bronchodilator use:** mepolizumab, 78.1% (± 20.9%); placebo, 77.6% (± 24.1%)
- **Baseline mean (SD) FEV$_1$/FVC ratio:** mepolizumab, 72.2% (± 9.6%); placebo, 67.7% (± 13.5%)
- 29 allocated to receive mepolizumab 750 mg, 32 to receive placebo

### Interventions
Intravenous mepolizumab (750 mg) versus matched placebo (150 mL of 0.9% saline) at monthly intervals for 1 year

### Outcomes
Reported as: "Primary outcome measure was the number of severe exacerbations per subject during the 50-week treatment phase. Secondary outcomes included a change in asthma symptoms, scores on the Asthma Quality of Life Questionnaire (AQLQ, in which scores range from 1 to 7, with lower values indicating more severe impairment and a change of 0.5 unit considered to be clinically important), forced expiratory volume in 1 second (FEV$_1$) after use of a bronchodilator, airway hyperresponsiveness, and eosinophil counts in the blood and sputum."

### Notes
Single centre trial conducted at Institute for Lung Health, Leicester, UK
Supported by GlaxoSmithKline

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<td>Reported as: &quot;A total of 61 of the 63 participants (one required an operation and one withdrew consent) who were screened started treatment and constituted the modified intention-to-treat population. Thirty-two participants were randomly assigned to receive placebo. Overall, 94.9% of treatment visits were completed. Participants who withdrew completed a mean of 4.6 treatment visits (38.3%).&quot;</td>
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*Leckie 2000*
### Methods

Randomised, double-blind, placebo-controlled trial

### Participants

Participants with mild allergic asthma

Reported as: “24 non-smoking men (mean age 27, range 18–45 years) with mild allergic asthma (as defined by the American Thoracic Society) and a history of episodic wheeze and shortness of breath. The patients were atopic, as defined by positive skin tests in response to common airborne allergens (Dermatophagoides pteronyssinus, mixed grass pollen and cat hair) and were maintained on short-acting inhaled 2-agonist treatment as required. Patients had neither worsening asthma nor a respiratory infection in the preceding 6 weeks. FEV$_1$ at baseline was at least 70% of the predicted value and there was a documented airway hyperresponsiveness to histamine, with a provocation concentration causing a 20% reduction in FEV$_1$ (PC$_{20}$) < 8 mg/mL.

Patients had documented early and late asthmatic responses (defined as a 15% reduction in FEV$_1$ on at least three occasions between 4 and 10 h after allergen) to inhaled incremental allergen challenge between 3 and 6 weeks before the study treatment was given.

- Mean age (SD): mepolizumab 10 mg/kg, 28.0 years (± 4.3); mepolizumab 2.5 mg/kg, 30.0 (± 4.1)
- Males: mepolizumab 10 mg/kg, 8; mepolizumab 2.5 mg/kg, 8; placebo, 8
- Baseline mean (SD) FEV$_1$, % predicted: mepolizumab 10 mg/kg, 82.0% (± 7.0%); mepolizumab 2.5 mg/kg, 90.3% (± 10.4%); placebo, 93.0% (± 9.6%)
- 8 allocated to receive mepolizumab 10 mg/kg (8 completed), 8 allocated to receive mepolizumab 2.5 mg/kg (7 completed) and 8 to receive placebo (8 completed)

### Interventions

Mepolizumab 10 mg/kg versus mepolizumab 2.5 mg/kg versus placebo

### Outcomes

Blood eosinophils, sputum eosinophils, histamine PC$_{20}$ (mg/mL), late asthmatic reaction (maximum % fall in FEV$_1$)

### Notes

16 week study conducted at 3 centres: Imperial College London, Southampton University and University of Amsterdam

Supported by SmithKline Beecham, UK

### Risk of bias table

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
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<td>Method of randomisation not reported</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
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</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Study reported as double blind</td>
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<tr>
<td>Blinding of outcome assessment (detection bias)</td>
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</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>1 subject lost to follow-up, all other data appears to be reported</td>
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### Nair 2009

Methods

Randomised, double-blind, placebo-controlled trial
Participants

Inclusion criteria: Adult patients, aged 18 to 70 years, who were followed as outpatients and who required a minimum dose of prednisone treatment (in addition to high-dose inhaled steroid treatment) to prevent frequent exacerbations associated with induced sputum eosinophilia. Patients were enrolled if, at screening and baseline visits, they demonstrated sputum eosinophilia and symptoms. The symptoms could affect activity and sleep but should not have been severe enough to be of concern to the treating physician. Both FEV$_1$ (after appropriately withholding bronchodilators before and after inhaled salbutamol 200 mcg) and methacholine PC$_{20}$ were measured, but these did not need to be abnormal since the prednisone was required for the control of eosinophilic bronchitis and any clinical consequences of this, and because bronchitis can occur without these features of asthma. On the same doses of corticosteroids for at least one month.

Exclusion criteria: pregnancy, breastfeeding or lack of effective contraception in females of childbearing potential or females who are postmenopausal < 1 year. Baseline predicted FEV$_1$ before bronchodilator of 40% or less. This lower FEV$_1$ was acceptable since chronic airflow limitation, secondary to the eosinophilic bronchitis or asthma, is not an exclusion criterion. Neither is current or ex-cigarette smoking provided that the best FEV$_1$ in these patients was >60% predicted normal, or the best FEV$_1$/VC ratio was >60% in the previous two years. Exposure to a relevant seasonal environmental allergen, known to worsen asthma control, during the study period. Respiratory tract infection in the 4 weeks before the baseline visit. Clinical exacerbation requiring extra prednisone treatment in the 4 weeks before visit 1. Other cardiac, pulmonary, renal or systemic diseases that in the investigator’s opinion could interfere with the study results or compromise participants’ safety. Previous participation in any study using anti-monoclonal drug.

9 patients were assigned to receive mepolizumab (administered in 5 monthly infusions of 750 mg each) and 11 patients to receive placebo.

- Mean age (SD): mepolizumab, 56.4 years (± 10.9); placebo, 58.2 years (± 7)
- Male: mepolizumab, 4; placebo, 8
- Mean (SD) duration of symptoms: mepolizumab, 13.3 years (± 10.3); placebo, 12.5 years (± 9.5)
- Baseline mean (SD) FEV$_1$ previous minimum (L): mepolizumab, 1.4 (± 0.6); placebo, 1.6 (± 0.5)
- Baseline mean (SD) FEV$_1$, % predicted: mepolizumab, 48% (± 17); placebo, 52% (± 13)

Interventions

5 intravenous doses of either mepolizumab (750 mg) or placebo (administered in 5 monthly infusions)

Outcomes

Primary outcome:
The prednisone-sparing effect of mepolizumab versus placebo as indicated by the absolute and percentage dose reduction possible without a clinical exacerbation (as measured by the JACQ in patients with asthma or by Likert symptom scores + FEV$_1$ in patients with eosinophilic bronchitis without asthma).

Secondary outcome measures:
The prednisone-sparing effect of mepolizumab or placebo as indicated by the absolute and percentage dose reduction possible without a clinical exacerbation, as measured by:

- % sputum eosinophils;
- FEV$_1$ % predicted and methacholine PC$_{20}$;
- blood eosinophils;
- amount of rescue salbutamol used;
- time to exacerbation.
**Notes**

26-week trial at Firestone Institute for Respiratory Health, St. Joseph’s Healthcare and Department of Medicine, McMaster University, Hamilton, ON, Canada
Supported by an unrestricted educational grant from GlaxoSmithKline

**Risk of bias table**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Computer-generated randomisation codes stratified patients into two groups of 10 according to the daily dose of prednisone they were receiving at the time of enrolment (&lt; 10 mg or ≥ 10 mg). Within each of the two groups, patients were equally divided among those receiving mepolizumab and those receiving placebo. When either group was filled, no additional patients were recruited for that group.</td>
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<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Randomisation codes were held by the pharmacy department, whose members were unaware of clinical details in the study groups.</td>
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<td>Blinding of participants and personnel (performance bias)</td>
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<td>Blinding of outcome assessment (detection bias)</td>
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<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Two of the patients were included in the study in error and were therefore excluded from some but not all of the analyses before the randomisation code was broken</td>
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<td>Low risk</td>
<td>No apparent indication of reporting bias</td>
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**Ortega 2014**

**Methods**

Randomised, double-blind, double-dummy, phase 3 study
### Participants

576 patients with recurrent asthma exacerbations and evidence of eosinophilic inflammation despite high doses of inhaled glucocorticoids to one of three study groups.

**Inclusion criteria:**
- Able to give written informed consent prior to participation in the study
- At least 12 years of age at visit 1 with a minimum weight of 45kg
- A well-documented requirement for regular treatment with high dose ICS in the 12 months prior to visit 1, with or without maintenance oral corticosteroids (OCS)
- Current treatment with an additional controller medication, besides ICS, for at least 3 months, or a documented failure in the past 12 months of an additional controller medication for at least 3 successive months
- Prior documentation of eosinophilic asthma or high likelihood of eosinophilic asthma
- At visit 1, a pre-bronchodilator FEV$_1$ < 80% (for participants ≥ 18 years of age), a pre-bronchodilator FEV$_1$ < 90% or FEV$_1$/FVC ratio < 0.8 (for participants 12 to 17 years of age)
- Previously confirmed history of two or more exacerbations requiring treatment with systemic corticosteroids
- Male or eligible female (females of childbearing potential must commit to consistent and correct use of an acceptable method of birth control)
- French participants will be included only if affiliated to or a beneficiary of a social security category

**Exclusion criteria:**
- Current smokers or former smokers with a smoking history of ≥ 10 pack-years
- Presence of a known pre-existing, clinically important lung condition other than asthma
- A current malignancy or previous history of malignancy in previous 12 months
- Known, pre-existing, unstable liver disease cirrhosis and known biliary abnormalities
- Known, pre-existing severe or clinically significant cardiovascular disease
- Known, pre-existing other concurrent clinically significant medical conditions that are uncontrolled with standard treatment
- Participants with any eosinophilic diseases
- QTc(F)$^a$ ≥ 450 ms or QTc(F) ≥ 480 ms
- A history of alcohol/substance abuse
- Known immunodeficiency
- Administration of omalizumab within 130 days of visit 1 or any other monoclonal antibody to treat inflammatory disease within 5 half-lives of visit 1
- Treatment with an investigational drug within the previous 30 days or 5 terminal phase half-lives of the drug, whichever is longer
- Allergy/intolerance to a monoclonal antibody or biologic therapy
- Pregnant or breastfeeding
- Known evidence of lack of adherence to controller medications, inability to follow physician's recommendations, or both
- Previous participation in any study with mepolizumab and administration of investigational product (including placebo)

### Interventions

Mepolizumab in a 75 mg intravenous dose versus mepolizumab in a 100 mg subcutaneous dose versus placebo every 4 weeks for 32 weeks

### Outcomes

**Primary outcome:**
- Number of clinically significant exacerbations of asthma per year

**Secondary outcomes:**
- Number of clinically significant exacerbations requiring hospitalisation (including intubation and admittance to an intensive care unit) or ED visits per year
- Mean change from baseline in clinic pre-bronchodilator FEV$_1$ at week 32
- Mean change from baseline in the SGRQ total score at week 32

### Notes

32-week treatment intervention, with 1 to 6 weeks run-in and 8-week followup.

Conducted in Baltimore, Middlesex, Ghent, Vancouver, Parma, Marseille and Paris
### Risk of bias table

<table>
<thead>
<tr>
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<td>Centralised computer-generated permuted block schedule</td>
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<td>Treatment allocations will be concealed via the RandAll system</td>
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<td>Mepolizumab and placebo were identical in appearance and were administered by a staff member who was unaware of the study group assignments.</td>
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<td>The study drugs were prepared by staff members who were aware of the study group assignments but were not involved in study assessments.</td>
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<td>Incomplete outcome data (attrition bias)</td>
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<td>6% (placebo), 8% (IV), 5% (SC) did not complete the study</td>
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<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All outcome measures reported</td>
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### Pavord 2012

<table>
<thead>
<tr>
<th>Methods</th>
<th>Multicentre, double-blind, placebo-controlled trial</th>
</tr>
</thead>
</table>
### Participants

People with severe asthma despite receiving high doses of standard asthma medications  

**Inclusion criteria:**  
- Male or female  
- Aged 12 to 65 years inclusive  
- Minimum weight 45 kg  
- Clinical features of severe refractory asthma  
- Well-documented requirement for high dose ICS (i.e. ≥ 880 mcg/day fluticasone propionate or equivalent daily) for at least 12 months  
- Use of additional controller medication in addition to high dose ICS for at least 12 months  
- Persistent airflow obstruction indicated by a pre-bronchodilator FEV$_1$ < 80% predicted at visit 1 or 2 or peak flow diurnal variability of > 20% on 3 or more days during the run-in  
- Airway inflammation likely to be eosinophilic in nature, demonstrated by either raised peripheral blood eosinophils (≥ 300/μL), sputum eosinophils (≥ 3%), exhaled nitric oxide (≥50 ppb) or prompt deterioration of asthma control following a ≤ 25% reduction in regular maintenance dose of ICS or OCS  
- History of ≥ 2 exacerbations requiring systemic corticosteroids in the previous 12 months  
- Evidence of asthma documented by airway reversibility, airway hyperresponsiveness or airflow variability  
- ECG assessment demonstrating QTc < 450 ms or QTc < 480 ms for patients with bundle branch block  
- Liver function tests on surrogate markers for liver disease, demonstrating ALT < 2 x ULN, AST < 2 x ULN, Alk Phos ≤ 1.5 x ULN, bilirubin ≤ 1.5 x ULN  
- Female of non-child-bearing potential or child-bearing potential with a negative pregnancy test at screening and prepared to use an acceptable method of contraception  
- Able to give written informed consent  
- Able to read, comprehend and write at a sufficient level to complete study materials  

**Exclusion Criteria:**  
- Current smokers or smoking history of ≥ 10 pack years  
- Clinically important lung condition other than asthma  
- Diagnosis or suspicion of malignancy  
- Unstable liver disease  
- Churg-Strauss syndrome  
- Use of methotrexate, troleandomycin, oral gold, cyclosporine, azathioprine or any experimental anti-inflammatory therapy within 3 months of screening  
- Administration of omalizumab (Xolair) or any other biological agent for the treatment of inflammatory disease within 6 months of visit 1  
- Regular use of OCS or systemic corticosteroids for diseases other than asthma within 12 months; any intra-articular, short-acting intramuscular corticosteroid within 1 month; or intramuscular, long-acting depot corticosteroid within 3 months  
- Allergy/intolerance to the excipients in the mepolizumab formulation  
- Administration of any investigational drug in previous 30 days or 5 terminal half-lives, whichever is longer  
- Pregnant, breastfeeding or planning to become pregnant  
- Clinically significant disease which is uncontrolled with standard treatment  
- History of alcohol misuse or substance abuse  
- Parasitic infestation within previous 6 months  
- Known immunodeficiency  
- Unable to follow instructions, use the electronic diary or peak flow meter  
- Known evidence of lack of adherence to controller medications, inability to follow physician’s recommendations, or both  
- Previous participation in a study of mepolizumab and received study medication within 90 days  
- 621 patients were randomised: 156 were assigned to 750 mg mepolizumab, 152 to 250 mg mepolizumab, 154 to 75 mg mepolizumab, and 159 to placebo  

### Interventions

13 total intravenous infusions of mepolizumab (750 mg), mepolizumab (250 mg), mepolizumab (75 mg) or placebo given every 4 weeks
MEP-AST Mepolizumab versus placebo for asthma

Outcomes

Primary outcome:
- Frequency of clinically significant exacerbations of asthma

Secondary outcomes:
- Time to first clinically significant exacerbation requiring oral or systemic corticosteroids, hospitalisation, and/or ED visits
- Frequency of exacerbations requiring hospitalisation (including intubation and admittance to an ICU) or ED visits
- Time to first exacerbation requiring hospitalisation or ED visit
- Frequency of investigator-defined exacerbations
- Time to first investigator-defined exacerbation
- Mean change from baseline in clinic pre-bronchodilator FEV₁ over the 52-week treatment period
- Mean change from baseline in clinic post-bronchodilator FEV₁ over the 52-week treatment period
- Mean change from baseline in ACQ score

Notes

52-week study conducted at 81 centres in 13 countries (Argentina, Australia, Canada, Chile, France, Germany, South Korea, Poland, Romania, Russia, Ukraine, the UK and the USA)
Supported by GlaxoSmithKline

Risk of bias table

<table>
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<tr>
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<td>Central telephone-based system and computer-generated randomly permuted block schedule stratified by whether treatment with oral corticosteroids was required</td>
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<td>(selection bias)</td>
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<td>Allocation concealment</td>
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<td>Mepolizumab and placebo were prepared by unmasked site staff who were not involved in study assessments</td>
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<td>(selection bias)</td>
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<tr>
<td>Blinding of participants and</td>
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<td>Mepolizumab and placebo were prepared by unmasked site staff who were not involved in study assessments. Both treatments were identical in appearance and were given to patients by a masked member of the site staff</td>
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<td>personnel (performance bias)</td>
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<td>Data analysts were masked to treatment allocation</td>
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<td>(detection bias)</td>
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<td>Incomplete outcome data</td>
<td>Low risk</td>
<td>All patients accounted for with information on reasons for having withdrawn. Some patients not included in results due to ‘poor efficacy’</td>
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<td>(attrition bias)</td>
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<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
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</table>

Footnotes

ACQ: Asthma Control Questionnaire; ALT: alanine aminotransferase; Alk Phos: alkaline phosphatase; AQLQ: Asthma Quality of Life Questionnaire; AST: aspartate aminotransferase; ECP: eosinophil cationic protein; ED: emergency department; FEV₁: Forcexpiratory volume in 1 second; FVC: forced vital capacity; HRQoL: health-related quality of life; ICS: inhaled corticosteroid; IL: interleukin; IV: intravenous; JACQ: Juniper Asthma Control Questionnaire; OCS: oral corticosteroids; PC₂₀: histamine provocative concentration causing a 20% drop in FEV₁; PEFR: peak expiratory flow rate; SC: subcutaneous; SD: standard deviation; SGRQ: St. George's Respiratory Questionnaire; ULN: Upper Limit of Normal; VC: vital capacity.

² QTc(F): a measure of the time between the start of the Q wave and the end of the T wave in the heart’s electrical cycle, corrected for the heart rate using Fredericia’s formula.

Characteristics of excluded studies

Alvarez-Cuesta 1994
<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
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<td>MEP-AST Mepolizumab versus placebo for asthma</td>
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<td><strong>Bel 2014</strong></td>
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<td>Kopp 2009</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Kopp 2013</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Kulus 2010</td>
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<td>Lanier 2003</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Lanier 2009</td>
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</tr>
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<td>Laviolette 2013</td>
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<td>Leynadier 2004</td>
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<tr>
<td>Lizaso 2008</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Massanari 2009</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Massanari 2010</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Mathur 2011</td>
<td>Study does not include Mepolizumab</td>
</tr>
<tr>
<td>Metzger 1998</td>
<td></td>
</tr>
<tr>
<td>Study Reference</td>
<td>Reason for exclusion</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Milgrom 1999</td>
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</tr>
<tr>
<td>Milgrom 2001</td>
<td>Study does not include mepolizumab</td>
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<td>Modlin 1977</td>
<td>Study does not include mepolizumab</td>
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<td>Moss 1987</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Nair 2010</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>NCT00802438</td>
<td>Non randomised study</td>
</tr>
<tr>
<td>NCT01366521</td>
<td>Phase 2 study comparing three doses of Mepolizumab. This trial does not have a placebo arm.</td>
</tr>
<tr>
<td>NCT01471327</td>
<td>Focus of study was on tolerability, pharmacokinetics and pharmacodynamics of single dose SB-240563 administered intravenously to Japanese healthy male subjects. Patients with asthma were not included in the study</td>
</tr>
<tr>
<td>NCT01691859</td>
<td>This study does not include a placebo group. Multi-centre, open-label, long term safety study with total sample receiving 100 milligrams (mg) mepolizumab administered subcutaneously (no control group).</td>
</tr>
<tr>
<td>NCT01842607</td>
<td>This study does not include a placebo group. Multi-centre, open-label, long term safety study with total sample receiving 100 milligrams (mg) mepolizumab administered subcutaneously (no control group).</td>
</tr>
<tr>
<td>NCT02135692</td>
<td>This study does not include a placebo group. Multi-center, open-label, long-term study of subcutaneously (SC) administered mepolizumab 100mg in addition to standard of care (SOC), in subjects with severe eosinophilic asthma</td>
</tr>
<tr>
<td>NCT02293265</td>
<td></td>
</tr>
<tr>
<td>Study Date</td>
<td>Reason for exclusion</td>
</tr>
<tr>
<td>---------------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>Niven 2008</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Noga 2003</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Noga 2008</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Noonan 2013</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Oba 2004</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Oh 2013</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Ohashi 1997</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Ohman 1984</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Ohta 2009</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Ong 2005</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Parker 2010</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Pauli 1984</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Piper 2013</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Prieto 2006</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Study</td>
<td>Reason for exclusion</td>
</tr>
<tr>
<td>-----------------</td>
<td>---------------------------------------</td>
</tr>
<tr>
<td>Pui 2010</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Rose 2009</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Sakamoto 1984</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Scheerens 2011</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Scheerens 2014</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Siergiejko 2011</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Silk 1998</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Silkoff 2004</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Simoes 2007</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Singh 2010</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Slavin 2009</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Soler 2001</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Sorkness 2013</td>
<td>Does not include Mepolizumab</td>
</tr>
<tr>
<td>Sthoeger 2007</td>
<td>Study does not include mepolizumab</td>
</tr>
</tbody>
</table>
### MEP-AST Mepolizumab versus placebo for asthma

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugaya 1994</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Swanson 2014</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Szymaniak 1998</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Tanaka 1993</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Terr 1969</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Van Rensen 2009</td>
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</tr>
<tr>
<td>Vignola 2004</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Wark 2003</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Wenzel 2009</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Wenzel 2013</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Zetterstrom 1972</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Zhu 2013</td>
<td>Study does not include mepolizumab</td>
</tr>
<tr>
<td>Zielen 2013</td>
<td>Study does not include mepolizumab</td>
</tr>
</tbody>
</table>

**Footnotes**

**Characteristics of ongoing studies**

- **NCT01520051 2012**
<table>
<thead>
<tr>
<th>Study name</th>
<th>Mepolizumab treatment for rhinovirus-induced asthma exacerbations (MATERIAL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised double blind trial</td>
</tr>
<tr>
<td>Participants</td>
<td>Mild allergic asthma patients with viral airway infections</td>
</tr>
<tr>
<td>Inclusion criteria:</td>
<td></td>
</tr>
<tr>
<td>- Age: from 18 to 50 years</td>
<td></td>
</tr>
<tr>
<td>- History of episodic chest tightness and wheezing</td>
<td></td>
</tr>
<tr>
<td>- Intermittent or mild persistent asthma according to the criteria of the Global Initiative for Asthma</td>
<td></td>
</tr>
<tr>
<td>- Non-smoking or stopped smoking more than 12 months ago and ≤ 5 pack-years</td>
<td></td>
</tr>
<tr>
<td>- Clinically stable, no history of exacerbations within 6 weeks prior to the study</td>
<td></td>
</tr>
<tr>
<td>- Steroid-naïve or those not currently on corticosteroids and who have not taken any corticosteroids by any dosing routes within 2 weeks prior to the study. Occasional usage of inhaled short-acting beta_2-agonists as rescue medication is allowed, prior to and during the study</td>
<td></td>
</tr>
<tr>
<td>- Baseline FEV_1 &gt; 80% of predicted</td>
<td></td>
</tr>
<tr>
<td>- Airway hyperresponsiveness, indicated by a positive acetyl-beta-methylcholine bromide (MeBr) challenge with PC_20 &lt; 9.8 mg/mL</td>
<td></td>
</tr>
<tr>
<td>- Positive skin prick test (SPT) to one or more of the 12 common aeroallergen extracts, defined as a wheal with an average diameter over 3 mm</td>
<td></td>
</tr>
<tr>
<td>- No other clinically significant abnormality on medical history and clinical examination</td>
<td></td>
</tr>
<tr>
<td>Exclusion Criteria:</td>
<td></td>
</tr>
<tr>
<td>- Presence of antibodies directed against RV16 in serum (titre &gt; 4), measured at visit 1</td>
<td></td>
</tr>
<tr>
<td>- History of clinical significant hypotensive episodes or symptoms of fainting, dizziness, or light-headedness</td>
<td></td>
</tr>
<tr>
<td>- Women who are pregnant, lactating or who have a positive urine pregnancy test at visit 1</td>
<td></td>
</tr>
<tr>
<td>- Chronic use of any other medication for treatment of lung disease other than short-acting beta_2-agonists</td>
<td></td>
</tr>
<tr>
<td>- Participation in any clinical investigational drug treatment protocol in previous 3 months</td>
<td></td>
</tr>
<tr>
<td>- Ongoing use of tobacco products of any kind or previous usage with ≥ 6 total pack-years</td>
<td></td>
</tr>
<tr>
<td>- Concomitant disease or condition which could interfere with the conduct of the study, or for which the treatment might interfere with the conduct of the study, or which would, in the opinion of the investigator, pose an unacceptable risk to the patient</td>
<td></td>
</tr>
<tr>
<td>- People with young children (&lt; 2 years)</td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
<td>3 monthly intravenous infusions of 750 mg versus 3 monthly intravenous infusions with saline</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary outcome measures:</td>
</tr>
<tr>
<td>- FEV_1 1 day prior and 6 days after RV16 challenge</td>
<td></td>
</tr>
<tr>
<td>- Questionnaire to score asthma and common cold complaints during 14 days following viral infection</td>
<td></td>
</tr>
<tr>
<td>Secondary outcome measures:</td>
<td></td>
</tr>
<tr>
<td>- Viral load on day 6 after viral infection</td>
<td></td>
</tr>
<tr>
<td>- Sputum eosinophils before and after mepolizumab infusion</td>
<td></td>
</tr>
<tr>
<td>- Cell influx in bronchoalveolar lavage fluid 6 days after viral infection</td>
<td></td>
</tr>
<tr>
<td>- Pro-inflammatory cytokines in bronchoalveolar lavage fluid 6 days after viral infection</td>
<td></td>
</tr>
<tr>
<td>- Antibody production 6 weeks after infection</td>
<td></td>
</tr>
</tbody>
</table>
A randomised, double-blind, placebo-controlled, parallel-group, multi-centre, 24-week study to evaluate the efficacy and safety of mepolizumab adjunctive therapy in subjects with severe eosinophilic asthma on markers of asthma control.

### Methods
Multicentre, placebo-controlled, double-blind, parallel-group study

### Participants
People with severe eosinophilic asthma. Approximately 780 participants with severe eosinophilic asthma will be screened to ensure the randomisation of 544 participants (272 participants per treatment group) into the study.

### Interventions
Mepolizumab 100 mg subcutaneously into the upper arm or thigh every 4 weeks for a period of 24 weeks (total of 6 doses) along with their respective standard care of treatment, versus placebo (0.9% sodium chloride) subcutaneously into the upper arm or thigh every 4 weeks for a period of 24 weeks (total of 6 doses) along with their respective standard care of treatment.

### Outcomes
- **Primary Outcome Measure:**
  - Mean change from baseline in St. George's Respiratory Questionnaire (SGRQ) score at week 24
- **Secondary Outcome Measures:**
  - Mean change from baseline in clinic pre-bronchodilator FEV\(_1\) at week 24
  - Percentage of participants achieving a 4 point or greater reduction from baseline in SGRQ score at week 24
  - Mean change from baseline in five-item Asthma Control Questionnaire (ACQ-5) score at week 24

### Starting date
December 2014

### Contact information
US GSK Clinical Trials Call Center: GSKClinicalSupportHD@gsk.com

### Notes
Estimated primary completion date: 2016

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**Footnotes**

- \(\text{FEV}_1\): Forced expiratory volume in 1 second;
- \(\text{PC}_{20}\): histamine provocative concentration causing a 20% drop in \(\text{FEV}_1\)

---

**Summary of findings tables**

### 1 Intravenous mepolizumab compared to placebo for asthma

<table>
<thead>
<tr>
<th>IV mepolizumab compared to placebo for asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient or population:</strong> adults with asthma of varying degrees of severity</td>
</tr>
<tr>
<td><strong>Settings:</strong> community</td>
</tr>
<tr>
<td><strong>Intervention:</strong> intravenous (IV) mepolizumab</td>
</tr>
<tr>
<td><strong>Comparison:</strong> placebo</td>
</tr>
</tbody>
</table>
### Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Change in HRQoL assessed with AQLQ.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Placebo</strong> IV mepolizumab <strong>Assumed risk</strong> The mean change in HRQoL ranged from 0.18 to 0.71 units</td>
</tr>
<tr>
<td><strong>Change in HRQoL assessed with SGRQ.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Placebo</strong> IV mepolizumab <strong>Assumed risk</strong> The mean change in HRQoL was − 9.0 units</td>
</tr>
<tr>
<td><strong>Rate of clinically significant exacerbations - 75 mg mepolizumab versus placebo.</strong></td>
<td></td>
<td>Rate ratio 0.52 (0.43 to 0.64)</td>
<td>690 (2 studies)</td>
<td>⬤ substrates (a) <strong>Comments</strong> Moderate Quality <strong>Trial participants had severe eosinophilic asthma</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Rate of clinically significant exacerbations - 250 mg mepolizumab versus placebo.</strong></td>
<td></td>
<td>Rate ratio 0.61 (0.46 to 0.81)</td>
<td>307 (1 study)</td>
<td>⬤ substrates (a) <strong>Comments</strong> Moderate Quality <strong>Trial participants had severe eosinophilic asthma</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Rate of clinically significant exacerbations - 750 mg mepolizumab versus placebo.</strong></td>
<td></td>
<td>Rate ratio 0.48 (0.36 to 0.64)</td>
<td>311 (1 study)</td>
<td>⬤ substrates (a) <strong>Comments</strong> Moderate Quality <strong>Trial participants had severe eosinophilic asthma</strong></td>
<td></td>
</tr>
<tr>
<td><strong>People with one or more exacerbations.</strong></td>
<td>264 per 1000</td>
<td>Risk ratio 0.67 (0.34 to 1.31)</td>
<td>467 (4 studies)</td>
<td>⬤ substrates (a,d) <strong>Comments</strong> Low Quality <strong>Variety of asthma severity in the trials</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Serious adverse events.</strong></td>
<td>82 per 1000</td>
<td>Risk ratio 0.49 (0.30 to 0.80)</td>
<td>1441 (5 studies)</td>
<td>⬤ substrates (a) <strong>Comments</strong> Moderate Quality <strong>Variety of asthma severity in the trials</strong></td>
<td></td>
</tr>
</tbody>
</table>

*The basis for the assumed risk is the mean control group risk across studies. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

**AQLQ:** Asthma Quality of Life Questionnaire; **CI:** Confidence interval; **HRQoL:** health-related quality of life; **IV:** intravenous; **RCT:** randomised controlled trial; **SGRQ:** St George's Respiratory Questionnaire.

**GRADE Working Group grades of evidence**

- **High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- **Very low quality:** We are very uncertain about the estimate.

**Footnotes**
The intravenous route is not currently licenced for mepolizumab; one point deducted for indirectness.

The mean difference is less than the clinical minimally important difference (0.5 units), and no responder analysis is available; one point deducted.

Placebo exacerbation rate per patient per year is the rounded mean of rate in the placebo arm of the two studies (0.43 and 1.75).

Wide confidence interval increases the uncertainty of this outcome; one point deducted.

2 Subcutaneous mepolizumab compared to placebo for asthma
### Subcutaneous mepolizumab compared to placebo for asthma

**Patient or population:** adults with severe eosinophilic asthma  
**Settings:** community  
**Intervention:** subcutaneous (SC) mepolizumab  
**Comparison:** placebo

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>SC mepolizumab</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Change in HRQoL assessed with SGRQ.  
Scale from: 0 to 100 (lower is better)  
Follow-up: 32 weeks | The mean HRQoL was −9.0 units | The mean HRQoL - SGRQ in the intervention group was 7 units fewer (10.19 fewer to 3.81 fewer) | 385 (1 RCT) | ⊕⊕⊕⊝ moderate<sup>a</sup> |          |
| Rate of exacerbations requiring admission  
Follow-up: 32 weeks | The mean rate of exacerbations requiring admission on placebo was 0.10 per patient per year | The mean rate of exacerbations requiring ED visit or admission in the intervention group was 0.07 less per patient per year (0.01 less to 0.09 less) | Rate ratio 0.31 (0.11 to 0.91) | 385 (1 RCT) | ⊕⊕⊕⊝ moderate<sup>a</sup> |          |
| Rate of exacerbations requiring ED or admission  
Follow-up: 32 weeks | The mean rate of exacerbations requiring ED or admission on placebo was 0.20 per patient per year | The mean rate of exacerbations requiring ED or admission in the intervention group was 0.12 less per patient per year (0.03 less to 0.16 less) | Rate ratio 0.39 (0.18 to 0.83) | 385 (1 RCT) | ⊕⊕⊕⊝ moderate<sup>a</sup> |          |
| Rate of clinically significant exacerbations  
Follow-up: 32 weeks | The mean rate of clinically significant exacerbations on placebo was 1.75 per patient per year | The mean rate of clinically significant exacerbations in the intervention group was 0.93 less per patient per year (0.65 less to 1.14 less) | Rate ratio 0.47 (0.35 to 0.63) | 385 (1 RCT) | ⊕⊕⊕⊝ moderate<sup>a</sup> |          |
| Asthma symptoms measured on Asthma Control Questionnaire  
Scale from: 0 to 6 (lower is better)<sup>b</sup>  
Follow-up: 32 weeks | The mean change in asthma symptoms was −0.5 units | The mean asthma symptoms in the intervention group was 0.44 units fewer (0.64 fewer to 0.24 fewer) | 385 (1 RCT) | ⊕⊕⊕⊝ low<sup>a,c</sup> |          |

*The basis for the **assumed risk** was the event rate in the placebo arm of the single included study. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; ED: emergency department; HRQoL: health-related quality of life; RCT: randomised controlled trial; SC: subcutaneous; SGRQ: St George’s Respiratory Questionnaire.

**Footnotes**

<sup>a</sup>This finding is from a single study so we do not know how well this will match further research; one point deducted.

<sup>b</sup>The minimal clinically important difference on this scale is 0.5 units.

<sup>c</sup>The mean difference is less than the clinical minimally important difference (0.5 units), and no responder analysis is
## Additional tables

### 1 Comparisons of study characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Baseline Asthma severity</th>
<th>Baseline treatment</th>
<th>SC or IV</th>
<th>Intervention (mepolizumab)</th>
<th>Follow-up</th>
<th>Primary and secondary outcomes</th>
<th>No. participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leckie 2000</td>
<td>RCT double-blind, placebo</td>
<td>Mild allergic asthma</td>
<td>SABA as required</td>
<td>IV</td>
<td>10 mg/kg versus 2.5 mg/kg versus placebo</td>
<td>16 weeks</td>
<td>Blood eosinophils, sputum eosinophils, histamine PC$_{20}$ (mg/mL), late asthmatic reaction (maximum % fall in FEV$_1$)</td>
<td>24</td>
</tr>
<tr>
<td>Buttner 2003</td>
<td>RCT parallel group, multicentre double blind</td>
<td>Mild or moderate asthma (FEV$_1$ 50-80% predicted)</td>
<td>1000 mcg BDP or equivalent and stable</td>
<td>IV</td>
<td>Three 750 or 250 mg or placebo every 4 weeks for 6 months</td>
<td>6 months</td>
<td>Blood eosinophil, ECP, interferon-c producing CD4 T-cells</td>
<td>19</td>
</tr>
<tr>
<td>Flood-Page 2003</td>
<td>2-centre double-blind, placebo-controlled, parallel-group study</td>
<td>Mild atopic (skin prick positive)$^\dagger$ asthma (FEV$_1$ &gt;70% predicted)</td>
<td>SABA as required and no corticosteroids in previous 8 weeks</td>
<td>IV</td>
<td>Three doses of either 750 mg$^\dagger$ or placebo over 20 weeks (at weeks 0, 4 and 8)</td>
<td>20 weeks</td>
<td>Airway eosinophils, bone marrow eosinophils, blood eosinophils, airway hyperresponsiveness, FEV$_1$, PEFR</td>
<td>24</td>
</tr>
<tr>
<td>Flood-Page 2007</td>
<td>Multicentre randomised, double-blind, placebo-controlled trial</td>
<td>Moderate asthma (FEV$_1$ between 50% and 80% predicted)</td>
<td>maximum dose (BDP) or equivalent, 1000 mcg/d</td>
<td>IV</td>
<td>Three doses of either 750 mg or 250 mg or placebo over 20 weeks (at weeks 0, 4 and 8)</td>
<td>20 weeks</td>
<td>Change from baseline morning PEFR recorded at weeks 12 and 20; asthma summary symptom scores; use of rescue medication such as albuterol (salbutamol); quality of life scores; asthma exacerbation rates; eosinophil counts in blood and sputum</td>
<td>362</td>
</tr>
<tr>
<td>Nair 2009</td>
<td>Randomised, double-blind, placebo-controlled trial. $^\dagger$</td>
<td>Eosinophilic asthma</td>
<td>Prednisolone treatment with high-dose ICS</td>
<td>IV</td>
<td>Five doses of either 750 mg or placebo (administered in 5 monthly infusions) $^\dagger$</td>
<td>26 weeks</td>
<td>Juniper ACQ in patients with asthma or by Likert symptom scores + FEV$_1$ in patients with eosinophilic bronchitis without asthma; the prednisone-sparing effect of mepolimuzab or placebo as indicated by the absolute and percentage dose reduction possible without a clinical exacerbation (defined as % sputum eosinophilia, FEV$<em>1$ % predicted and methacholine PC$</em>{20}$); blood eosinophils; frequency of rescue salbutamol use; time to exacerbation</td>
<td>20</td>
</tr>
</tbody>
</table>
## MEP-AST Mepolizumab versus placebo for asthma

### Study Design

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Baseline Asthma severity</th>
<th>Baseline treatment</th>
<th>SC or IV</th>
<th>Intervention (mepolizumab)</th>
<th>Follow-up</th>
<th>Primary and secondary outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haldar 2009</td>
<td>RCT double-blind, placebo, parallel-group</td>
<td>Eosinophilic asthma and exacerbations</td>
<td>Sputum eosinophilia of more than 3% despite high-dose ICS treatment, and at least two exacerbations in previous 12 months</td>
<td>IV</td>
<td>750 mg versus matched placebo (150 mL of 0.9% saline) at monthly intervals for 1 year</td>
<td>50 weeks</td>
<td>Severe exacerbations per person; secondary outcomes included a change in asthma symptoms (AQLQ); FEV₁ after use of a bronchodilator; airway hyperresponsiveness; eosinophil counts in the blood, sputum</td>
</tr>
<tr>
<td>Pavord 2012</td>
<td>Multicentre, double-blind, placebo-controlled trial</td>
<td>Eosinophilic asthma and exacerbations</td>
<td>High dose ICS (i.e. ≥ 880 mcg/day FP or equivalent daily) for at least 12 months</td>
<td>IV</td>
<td>13 infusions in total given every 4 weeks of 750 mg, 250 mg, 75 mg or placebo</td>
<td>52 weeks</td>
<td>Exacerbations; time to first clinically significant exacerbation; frequency of exacerbations requiring hospitalisation; time to first exacerbation requiring hospitalisation or ED visit; mean change from baseline in clinic pre-bronchodilator FEV₁; mean change from baseline in clinic post-bronchodilator FEV₁; mean change from baseline in ACQ score</td>
</tr>
<tr>
<td>Ortega 2014</td>
<td>Randomised, double-blind, double-dummy, phase 3 study</td>
<td>Persistent eosinophilic asthma</td>
<td>High dose ICS in the 12 months prior to visit 1 with or without maintenance OCS</td>
<td>IV and SC</td>
<td>75 mg IV dose versus 100 mg SC dose versus placebo every 4 weeks for 32 weeks</td>
<td>32 weeks</td>
<td>Exacerbations per year; mean change from baseline in clinic pre-bronchodilator FEV₁ at week 32; mean change from baseline in the SGRQ total score at week 32</td>
</tr>
</tbody>
</table>

### Footnotes

ACQ: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; BDP: beclomethasone dipropionate; ECP: eosinophil cationic protein; ED: emergency department; FEV₁: Forced expiratory volume in 1 second; FP: fluticasone propionate; ICS: inhaled corticosteroid; IV: intravenous; PC₂₀: histamine provocative concentration causing a 20% drop in FEV₁; PEFR: peak expiratory flow rate; RCT: randomised controlled trial; SABA: short-acting beta-agonists; SC: subcutaneous; SGRQ: St George's Respiratory Questionnaire.

## 2 Lung function

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Pre-dose median (IQR)</th>
<th>Post-dose median (IQR)</th>
<th>Median difference</th>
<th>P value (between groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flood-Page 2003</td>
<td>FEV₁ L/s</td>
<td>3.05 (2.69 to 3.28)</td>
<td>3.1 (2.82 to 3.85)</td>
<td>0.15</td>
<td>0.22</td>
</tr>
<tr>
<td>Flood-Page 2003</td>
<td>Morning PEFR L/min</td>
<td>433 (402 to 497)</td>
<td>436 (417 to 503)</td>
<td>21</td>
<td>0.09</td>
</tr>
</tbody>
</table>

### Footnotes

FEV₁: Forced expiratory volume in 1 second; IQR: interquartile range; PEFR: peak expiratory flow rate

## 3 Eosinophils from Flood-Page 2003
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre-dose</td>
<td>Post-dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>median (IQR)</td>
<td>median (IQR)</td>
<td></td>
</tr>
<tr>
<td>BALF (% cell type on cytospin)</td>
<td>11</td>
<td>13</td>
<td>0.4</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>1.4 (0.9 to 10.2)</td>
<td>0.3 (0.01 to 0.8)</td>
<td>1.2 (0.2 to 6)</td>
</tr>
</tbody>
</table>

**Footnotes**

BALF: bronchoalveolar lavage fluid; IQR: interquartile range

### 4 Eosinophils from Haldar 2009

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Percentage</td>
<td>Percentage</td>
<td></td>
</tr>
<tr>
<td>Geometric mean sputum eosinophil % during exacerbation</td>
<td>291.5%</td>
<td>324.4%</td>
<td>0.005</td>
</tr>
<tr>
<td>Sputum eosinophil count &gt;3% during exacerbation (% of episodes)</td>
<td>2936%</td>
<td>3259%</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**Footnotes**

5 Sputum eosinophil results from Leckie 2000

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention Mepolizumab</th>
<th>Intervention Mepolizumab</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(10 mg/kg)</td>
<td>(2.5 mg/kg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=8</td>
<td>N=7</td>
<td></td>
</tr>
<tr>
<td>Day −13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference in blood eosinophils vs placebo pre-allergen</td>
<td>0.08 (− 0.09 to 0.26), P = 0.4960</td>
<td>0.18 (0.01 to 0.36), P = 0.0292</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 8</td>
<td>Day 9</td>
<td>Day 30</td>
</tr>
<tr>
<td></td>
<td>0.17 (0.04 to 0.30), P = 0.0054</td>
<td>0.01 (− 0.16 to 0.19), P = 1.00</td>
<td>0.02 (− 0.14 to 0.18), P = 1.00</td>
</tr>
<tr>
<td></td>
<td>0.21 (0.10 to 0.33), P &lt; 0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day −13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference in blood eosinophils vs placebo post-allergen</td>
<td>0.38 (0.07 to 0.69), P = 0.0144</td>
<td>0.23 (− 0.11 to 0.58), P = 0.2136</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 9</td>
<td>Day 30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.34 (0.13 to 0.55), P = 0.0006</td>
<td>0.32 (0.11 to 0.53), P = 0.0012</td>
<td>0.43 (0.22 to 0.65), P = 0.0002</td>
</tr>
<tr>
<td></td>
<td>0.49 (0.28 to 0.7), P &lt; 0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day −13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference in sputum eosinophils vs placebo</td>
<td>− 2.0 (− 16.2 to 12.3), P = 1.00</td>
<td>− 2.1 (− 16.3 to 12.2), P = 1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 9</td>
<td>Day 30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11.3 (2.6 to 20.1), P = 0.0076</td>
<td>5.0 (− 5.9 to 16.0), P = 0.6108</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12.1 (3.1 to − 21.0), P = 0.0050</td>
<td>5.9 (− 5.0 to 16.8), P = 0.4454</td>
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</table>

**Footnotes**

6 Sputum eosinophil results from Nair 2009

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Visit</th>
<th>Intervention</th>
<th>Control</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>median (range)</td>
<td>median (range)</td>
<td></td>
</tr>
<tr>
<td>Sputum eosinophils (%) median</td>
<td>Visit 1</td>
<td>9</td>
<td>114.0 (0 to 35.3)</td>
<td>P &lt; 0.05 compared to baseline</td>
</tr>
<tr>
<td></td>
<td>4 weeks after first dose</td>
<td>14.0 (range 0 to 4.0)</td>
<td>10.0 (0 to 16.3)</td>
<td>P &lt; 0.05 compared to baseline</td>
</tr>
<tr>
<td>Blood eosinophils (x 10^9/L)</td>
<td>Visit 1</td>
<td>9</td>
<td>11352.1 (± 253.7)</td>
<td>P &lt; 0.05 compared to baseline</td>
</tr>
<tr>
<td></td>
<td>4 weeks after first dose</td>
<td>949.5 (37.5)</td>
<td>10295.8 (± 207.4)</td>
<td>P &lt; 0.05 compared to baseline</td>
</tr>
</tbody>
</table>

**Footnotes**
References to studies

Included studies

**Buttner 2003**

**Flood-Page 2003**
Flood-Page PT, Menzies-Gow AN, Kay AB, Robinson DS. Eosinophil's role remains uncertain as anti-interleukin-5 only partially depletes numbers in asthmatic airway [comment]. American Journal of Respiratory and Critical Care Medicine 2003;167(2):199-204. [CRS-ID: 4900100000013790; Other: 4900100000013790]

**Buttner 2003**

**Flood-Page 2003**
Flood-Page PT, Menzies-Gow AN, Kay AB, Robinson DS. Eosinophil's role remains uncertain as anti-interleukin-5 only partially depletes numbers in asthmatic airway [comment]. American Journal of Respiratory and Critical Care Medicine 2003;167(2):199-204. [CRS-ID: 4900100000013790; Other: 4900100000013790]

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**Fahy 1999**
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Gauvreau 2014a

Gauvreau 2014b

Gauvreau 2014c

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MEP-AST Mepolizumab versus placebo for asthma

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**Other references**

**Additional references**

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**Higgins 2011**

**Kandane-Rathnayake 2009**

**Krishnan 2006**

**Liu 2013**

**Masoli 2004**

**NHS 2011**

**NIH 2007**

**Patel 2008**

**RevMan**

**WHO 2007**

**WHO 2011**

**Wu 2007**

**Other published versions of this review**
**Classification pending references**

**Data and analyses**

**1 IV Mepolizumab versus placebo**

<table>
<thead>
<tr>
<th>Outcome or Subgroup</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical Method</th>
<th>Effect Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Health-related quality of life (AQLQ)</td>
<td>2</td>
<td>677</td>
<td>Mean Difference(IV, Random, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>1.1.1 AQLQ</td>
<td></td>
<td></td>
<td>Mean Difference(IV, Random, 95% CI)</td>
<td>0.21[-0.01, 0.44]</td>
</tr>
<tr>
<td>1.2 Health-related quality of life (SGRQ)</td>
<td>1</td>
<td></td>
<td>Mean Difference(IV, Random, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>1.2.1 SGRQ</td>
<td></td>
<td></td>
<td>Mean Difference(IV, Random, 95% CI)</td>
<td>-6.40[-9.65, -3.15]</td>
</tr>
<tr>
<td>1.3 Rate of clinically significant exacerbations</td>
<td>2</td>
<td>Rate Ratio(IV, Random, 95% CI)</td>
<td>Subtotals only</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>---</td>
<td>-------------------------------</td>
<td>---------------</td>
<td></td>
</tr>
<tr>
<td>1.3.1 75 mg mepolizumab versus placebo</td>
<td>2</td>
<td>690</td>
<td>Rate Ratio(IV, Random, 95% CI)</td>
<td>0.52[0.43, 0.64]</td>
</tr>
<tr>
<td>1.3.2 250 mg mepolizumab versus placebo</td>
<td>1</td>
<td>307</td>
<td>Rate Ratio(IV, Random, 95% CI)</td>
<td>0.61[0.46, 0.81]</td>
</tr>
<tr>
<td>1.3.3 750 mg mepolizumab versus placebo</td>
<td>1</td>
<td>311</td>
<td>Rate Ratio(IV, Random, 95% CI)</td>
<td>0.48[0.36, 0.64]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1.4 Rate of exacerbations requiring admission</th>
<th>2</th>
<th>Rate Ratio(IV, Random, 95% CI)</th>
<th>Subtotals only</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.4.1 75 mg mepolizumab versus placebo</td>
<td>2</td>
<td>690</td>
<td>Rate Ratio(IV, Random, 95% CI)</td>
</tr>
<tr>
<td>1.4.2 250 mg mepolizumab versus placebo</td>
<td>1</td>
<td>307</td>
<td>Rate Ratio(IV, Random, 95% CI)</td>
</tr>
<tr>
<td>1.4.3 750 mg mepolizumab versus placebo</td>
<td>1</td>
<td>311</td>
<td>Rate Ratio(IV, Random, 95% CI)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>1.5 Rate of exacerbations requiring ED or admission</th>
<th>2</th>
<th>Rate Ratio(IV, Random, 95% CI)</th>
<th>Subtotals only</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5.1 75 mg mepolizumab versus placebo</td>
<td>2</td>
<td>690</td>
<td>Rate Ratio(IV, Random, 95% CI)</td>
</tr>
<tr>
<td>1.5.2 250 mg mepolizumab versus placebo</td>
<td>1</td>
<td>307</td>
<td>Rate Ratio(IV, Random, 95% CI)</td>
</tr>
<tr>
<td>1.5.3 750 mg mepolizumab versus placebo</td>
<td>1</td>
<td>311</td>
<td>Rate Ratio(IV, Random, 95% CI)</td>
</tr>
</tbody>
</table>

| 1.6 People with one or more exacerbations         | 4 | 467                          | Risk Ratio(M-H, Random, 95% CI) | 0.67[0.34, 1.31] |

| 1.7 Serious adverse events                       | 5 | 1441                         | Risk Ratio(M-H, Random, 95% CI) | 0.49[0.30, 0.80] |

<table>
<thead>
<tr>
<th>1.8 FEV1 (litres)</th>
<th>1</th>
<th></th>
<th>Mean Difference(IV, Random, 95% CI)</th>
<th>Subtotals only</th>
</tr>
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<tbody>
<tr>
<td>1.8.1 250 mg mepolizumab versus placebo</td>
<td>1</td>
<td>246</td>
<td>Mean Difference(IV, Random, 95% CI)</td>
<td>-0.03[-0.13, 0.07]</td>
</tr>
<tr>
<td>1.8.2 750 mg mepolizumab versus placebo</td>
<td>1</td>
<td>242</td>
<td>Mean Difference(IV, Random, 95% CI)</td>
<td>0.02[-0.10, 0.14]</td>
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</table>

<table>
<thead>
<tr>
<th>1.9 PEFR (L/min)</th>
<th>1</th>
<th></th>
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<th>Subtotals only</th>
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<tbody>
<tr>
<td>1.9.1 250 mg mepolizumab versus placebo</td>
<td>1</td>
<td>246</td>
<td>Mean Difference(IV, Random, 95% CI)</td>
<td>13.49[0.71, 26.27]</td>
</tr>
<tr>
<td>1.9.2 750 mg mepolizumab versus placebo</td>
<td>1</td>
<td>242</td>
<td>Mean Difference(IV, Random, 95% CI)</td>
<td>3.42[-9.40, 16.24]</td>
</tr>
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<table>
<thead>
<tr>
<th>1.10 Post bronchodilator FEV1 (L)</th>
<th>3</th>
<th></th>
<th>Mean Difference(IV, Random, 95% CI)</th>
<th>No totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.10.1 6 weeks</td>
<td>1</td>
<td></td>
<td>Mean Difference(IV, Random, 95% CI)</td>
<td>No totals</td>
</tr>
<tr>
<td>1.10.2 32 weeks</td>
<td>1</td>
<td></td>
<td>Mean Difference(IV, Random, 95% CI)</td>
<td>No totals</td>
</tr>
<tr>
<td>1.10.3 1 year</td>
<td>1</td>
<td></td>
<td>Mean Difference(IV, Random, 95% CI)</td>
<td>No totals</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1.11 Percentage predicted FEV1 after bronchodilation</th>
<th>1</th>
<th></th>
<th>Mean Difference(IV, Random, 95% CI)</th>
<th>No totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.11.1 6 weeks</td>
<td>1</td>
<td></td>
<td>Mean Difference(IV, Random, 95% CI)</td>
<td>No totals</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1.12 Pre-bronchodilator FEV1 (L) at week 32</th>
<th>1</th>
<th></th>
<th>Mean Difference(IV, Random, 95% CI)</th>
<th>No totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.12.1 75 mg mepolizumab versus placebo</td>
<td>1</td>
<td></td>
<td>Mean Difference(IV, Random, 95% CI)</td>
<td>No totals</td>
</tr>
</tbody>
</table>
### 1.13 Pre-bronchodilator FEV$_1$ (mL) at week 52

<table>
<thead>
<tr>
<th>Outcome or Subgroup</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical Method</th>
<th>Effect Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.13.1 75 mg mepolizumab versus placebo</td>
<td>1</td>
<td>308</td>
<td>Mean Difference(IV, Random, 95% CI)</td>
<td>61.00[-39.00, 161.00]</td>
</tr>
<tr>
<td>1.13.2 250 mg mepolizumab versus placebo</td>
<td>1</td>
<td>307</td>
<td>Mean Difference(IV, Random, 95% CI)</td>
<td>81.00[-18.51, 180.51]</td>
</tr>
<tr>
<td>1.13.3 750 mg mepolizumab versus placebo</td>
<td>1</td>
<td>311</td>
<td>Mean Difference(IV, Random, 95% CI)</td>
<td>56.00[-43.00, 155.00]</td>
</tr>
</tbody>
</table>

### 1.14 Late asthmatic reaction (maximum % fall in FEV1)

<table>
<thead>
<tr>
<th>Outcome or Subgroup</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical Method</th>
<th>Effect Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.14.1 2.5 mg/kg mepolizumab versus placebo</td>
<td>1</td>
<td>16</td>
<td>Mean Difference(IV, Random, 95% CI)</td>
<td>3.50[-3.46, 10.46]</td>
</tr>
<tr>
<td>1.14.2 7.5 mg/kg mepolizumab versus placebo</td>
<td>1</td>
<td>16</td>
<td>Mean Difference(IV, Random, 95% CI)</td>
<td>0.30[-6.50, 7.10]</td>
</tr>
</tbody>
</table>

### 1.15 Asthma symptoms

<table>
<thead>
<tr>
<th>Outcome or Subgroup</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical Method</th>
<th>Effect Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.15.1 75 mg mepolizumab versus placebo</td>
<td>2</td>
<td>690</td>
<td>Mean Difference(IV, Random, 95% CI)</td>
<td>-0.30[-0.55, -0.04]</td>
</tr>
<tr>
<td>1.15.2 250 mg mepolizumab versus placebo</td>
<td>2</td>
<td>553</td>
<td>Mean Difference(IV, Random, 95% CI)</td>
<td>-0.24[-0.48, 0.01]</td>
</tr>
<tr>
<td>1.15.3 750 mg mepolizumab versus placebo</td>
<td>4</td>
<td>631</td>
<td>Mean Difference(IV, Random, 95% CI)</td>
<td>-0.02[-0.57, 0.54]</td>
</tr>
<tr>
<td>1.16 Asthma symptoms (JACQ)</td>
<td>2</td>
<td>80</td>
<td>Mean Difference(IV, Random, 95% CI)</td>
<td>-0.04[-0.42, 0.35]</td>
</tr>
</tbody>
</table>

### Figures

Figure 1

Figures

Figure 1
**Caption**
Study flow diagram

**Figure 2**

<table>
<thead>
<tr>
<th>Risk of bias item</th>
<th>Percentage Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>![Diagram]</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>![Diagram]</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>![Diagram]</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>![Diagram]</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>![Diagram]</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>![Diagram]</td>
</tr>
</tbody>
</table>

**Caption**
Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

**Figure 3**
Risk of bias summary: review authors’ judgements about each risk of bias item for each included study.

Sources of support

Internal sources
- No sources of support provided

External sources
- National Institute for Health Research (SJM), UK

Feedback

Appendices

1 Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

<table>
<thead>
<tr>
<th>Database</th>
<th>Frequency of search</th>
</tr>
</thead>
<tbody>
<tr>
<td>CENTRAL (the Cochrane Library)</td>
<td>Monthly</td>
</tr>
<tr>
<td>MEDLINE (Ovid)</td>
<td>Weekly</td>
</tr>
<tr>
<td>EMBASE (Ovid)</td>
<td>Weekly</td>
</tr>
<tr>
<td>PsycINFO (Ovid)</td>
<td>Monthly</td>
</tr>
<tr>
<td>CINAHL (EBSCO)</td>
<td>Monthly</td>
</tr>
<tr>
<td>AMED (EBSCO)</td>
<td>Monthly</td>
</tr>
</tbody>
</table>

Hand-searches: core respiratory conference abstracts
<table>
<thead>
<tr>
<th>Conference</th>
<th>Years searched</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Academy of Allergy, Asthma and Immunology (AAAAI)</td>
<td>2001 onwards</td>
</tr>
<tr>
<td>American Thoracic Society (ATS)</td>
<td>2001 onwards</td>
</tr>
<tr>
<td>Asia Pacific Society of Respirology (APSR)</td>
<td>2004 onwards</td>
</tr>
<tr>
<td>British Thoracic Society Winter Meeting (BTS)</td>
<td>2000 onwards</td>
</tr>
<tr>
<td>Chest Meeting</td>
<td>2003 onwards</td>
</tr>
<tr>
<td>International Primary Care Respiratory Group Congress (IPCRG)</td>
<td>2002 onwards</td>
</tr>
<tr>
<td>Thoracic Society of Australia and New Zealand (TSANZ)</td>
<td>1999 onwards</td>
</tr>
</tbody>
</table>

MEDLINE search strategy used to identify trials for the CAGR

**Asthma search**
1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.
4. Respiratory Sounds/
5. wheez$.mp.
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp.
9. bronchoconstrict$.mp.
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.
16. or/1-15

**Filter to identify RCTs**
1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases.

**2 Search Strategy for Cochrane Airways Group Register**
#1 AST:MISC1
#2 MeSH DESCRIPTOR Asthma Explode All
#3 asthma*:ti,ab
#4 #1 or #2 or #3
#5 MeSH DESCRIPTOR Antibodies, Monoclonal
#6 MeSH DESCRIPTOR Antibodies, Monoclonal, Humanized
#7 mepolizumab
#8 SB24056 or SB-24056
#9 human* NEAR2 monoclonal* NEAR2 antibod*
#10 Bosatria
#11 #5 or #6 or #7 or #8 or #9 or #10
#12 #4 and #11

[In search line #1, MISC1 denotes the field where the reference has been coded for condition, in this case, asthma]